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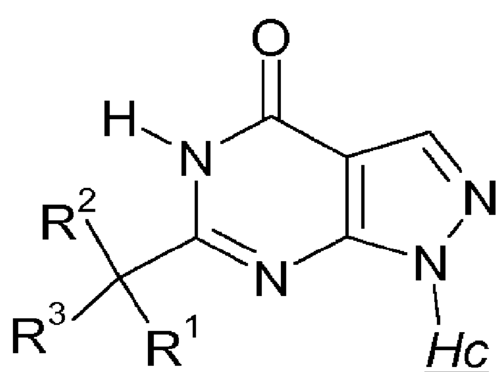
(54) Title: 1-HETEROCYCLYL-1, 5-DIHYDRO-PYRAZOLO [3, 4-D] PYRIMIDIN-4-ONE DERIVATIVES AND THEIR USE AS PDE9A MODULATORS



(I)

(57) Abstract: The invention relates to novel 1,6-disubstituted pyrazolopyrimidinones of formula (I), in which is a tetrahydropyranyl-group and R^1 is the group V-W-*, whereby V and W independently of each other may be an aryl group or an heteroaryl group, which independently of each other may optionally be substituted. According to one aspect of the invention the new compounds are for use as medicaments or for the manufacture of medicaments, in particular medicaments for the treatment of conditions concerning deficits in perception, concentration, learning or memory. The new compounds are also for the manufacture of medicaments and / or for use in the treatment of e.g. Alzheimer's disease, in particular for cognitive impairment associated with Alzheimer's disease.

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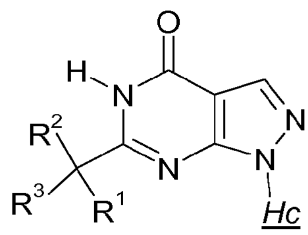
1-HETEROCYCLYL-1,5-DIHYDRO-PYRAZOLO[3,4-D]PYRIMIDIN-4-ONE DERIVATIVES AND THEIR USE AS PDE9A MODULATORS

The invention relates to novel 1,6-disubstituted pyrazolopyrimidinones of formula (I),



(I)

in which ***Hc*** is a tetrahydropyranyl-group and $\mathbf{R^1}$ is the group V-W-*, whereby V and W independently of each other may be an aryl group or an heteroaryl group, which independently of each other may optionally be substituted.

According to one aspect of the invention the new compounds are for use as medicaments or for the manufacture of medicaments, in particular medicaments for the treatment of conditions concerning deficits in perception, concentration, learning or memory. Such conditions may for example be associated with Alzheimer's disease. The new compounds are also for example for the manufacture of medicaments and / or for use in the treatment of e.g. Alzheimer's disease, in particular for cognitive impairment associated with Alzheimer's disease. The compounds of the invention are PDE 9 inhibitors.

BACKGROUND OF THE INVENTION

The inhibition of phosphodiesterase 9A (PDE9A) is one of the currents concepts to find new access paths to the treatment of cognitive impairments due to CNS disorders like Alzheimer's Disease or due to any other neurodegenerative process of the brain. With the present invention, new compounds that follow this concept are presented.

Phosphodiesterase 9A is one member of the wide family of phosphodiesterases. These enzymes modulate the levels of the cyclic nucleotides 5'-3' cyclic adenosine monophosphate (cAMP) and 5'-3' cyclic guanosine monophosphate (cGMP). These

cyclic nucleotides (cAMP and cGMP) are important second messengers and therefore play a central role in cellular signal transduction cascades. Each of them reactivates inter alia, but not exclusively, protein kinases. The protein kinase activated by cAMP is called protein kinase A (PKA), and the protein kinase activated by cGMP is called protein kinase G (PKG). Activated PKA and PKG are able in turn to phosphorylate a number of cellular effector proteins (e.g. ion channels, G-protein-coupled receptors, structural proteins, transcription factors). It is possible in this way for the second messengers cAMP and cGMP to control a wide variety of physiological processes in a wide variety of organs. However, the cyclic nucleotides are also able to act directly on effector molecules. Thus, it is known, for example, that cGMP is able to act directly on ion channels and thus is able to influence the cellular ion concentration (review in: Wei *et al.*, *Prog. Neurobiol.*, **1998**, *56*, 37-64). The phosphodiesterases (PDE) are a control mechanism for the activity of cAMP and cGMP and thus in turn for the corresponding physiological processes. PDEs hydrolyse the cyclic monophosphates to the inactive monophosphates AMP and GMP. Currently, 11 PDE families have been defined on the basis of the sequence homology of the corresponding genes. Individual PDE genes within a family are differentiated by letters (e.g. PDE1A and PDE1B). If different splice variants within a gene also occur, this is then indicated by an additional numbering after the letters (e.g. PDE1A1).

Human PDE9A was cloned and sequenced in 1998. The amino acid identity with other PDEs does not exceed 34% (PDE8A) and is never less than 28% (PDE5A). With a Michaelis-Menten constant (Km) of 170 nanomolar (nM), PDE9A has high affinity for cGMP. In addition, PDE9A is selective for cGMP (Km for cAMP=230 micromolar (µM). PDE9A has no cGMP binding domain, suggesting that the enzyme activity is not regulated by cGMP. It was shown in a Western blot analysis that PDE9A is expressed in humans inter alia in testes, brain, small intestine, skeletal muscle, heart, lung, thymus and spleen. The highest expression was found in the brain, small intestine, kidney, prostate, colon, and spleen (Fisher *et al.*, *J. Biol. Chem.*, **1998**, *273* (25), 15559-15564; Wang *et al.*, *Gene*, **2003**, *314*, 15-27). The gene for human PDE9A is located on chromosome 21q22.3 and comprises 21

exons. 4 alternative splice variants of PDE9A have been identified (Guipponi *et al.*, *Hum. Genet.*, **1998**, *103*, 386-392). Classical PDE inhibitors do not inhibit human PDE9A. Thus, IBMX, dipyridamole, SKF94120, rolipram and vinpocetine show no inhibition on the isolated enzyme in concentrations of up to 100 micromolar (μM). An IC50 of 35 micromolar (μM) has been demonstrated for zaprinast (Fisher *et al.*, *J. Biol. Chem.*, **1998**, *273* (25), 15559-15564).

Murine PDE9A was cloned and sequenced in 1998 by Soderling *et al.* (*J. Biol. Chem.*, **1998**, *273* (19), 15553-15558). This has, like the human form, high affinity for cGMP with a Km of 70 nanomolar (nM). Particularly high expression was found in the mouse kidney, brain, lung and liver. Murine PDE9A is not inhibited by IBMX in concentrations below 200 micromolar either; the IC50 for zaprinast is 29 micromolar (Soderling *et al.*, *J. Biol. Chem.*, **1998**, *273* (19), 15553-15558). It has been found that PDE9A is strongly expressed in some regions of the rat brain. These include olfactory bulb, hippocampus, cortex, basal ganglia and basal forebrain (Andreeva *et al.*, *J. Neurosci.*, **2001**, *21* (22), 9068-9076). The hippocampus, cortex and basal forebrain in particular play an important role in learning and memory processes. As already mentioned above, PDE9A is distinguished by having particularly high affinity for cGMP. PDE9A is therefore active even at low physiological concentrations, in contrast to PDE2A (Km=10 micromolar (μM); Martins *et al.*, *J. Biol. Chem.*, **1982**, *257*, 1973-1979), PDE5A (Km=4 micromolar (μM); Francis *et al.*, *J. Biol. Chem.*, **1980**, *255*, 620-626), PDE6A (Km=17 micromolar; Gillespie and Beavo, *J. Biol. Chem.*, **1988**, *263* (17), 8133-8141) and PDE11A (Km=0.52 micromolar; Fawcett *et al.*, *Proc. Nat. Acad. Sci.*, **2000**, *97* (7), 3702-3707). In contrast to PDE2A (Murashima *et al.*, *Biochemistry*, **1990**, *29*, 5285-5292), the catalytic activity of PDE9A is not increased by cGMP because it has no GAF domain (cGMP-binding domain via which the PDE activity is allosterically increased) (Beavo *et al.*, *Current Opinion in Cell Biology*, **2000**, *12*, 174-179). PDE9A inhibitors may therefore lead to an increase in the baseline cGMP concentration.

This outline will make it evident that PDE9A engages into specific physiological processes in a characteristic and unique manner, which distinguish the role of PDE9A characteristically from any of the other PDE family members.

WO04099210 discloses 6-arylmethyl-substituted pyrazolopyrimidinones which are PDE9 inhibitors. The compounds do not have a non-aromatic heterocyclic moiety in the 1 position of the pyrazolopyrimidine.

WO04096811 discloses heterocyclic bicycles as PDE9 inhibitors for the treatment of diabetes, including type 1 and type 2 diabetes, hyperglycemia, dyslipidemia, impaired glucose tolerance, metabolic syndrome, and/or cardiovascular disease.
Other prior art is directed to chemically similar nucleoside derivatives. As examples it is referred to WO02057425, which discloses nucleosides derivatives, which are inhibitors of RNA-dependent RNA viral polymerase, or WO01060315, which discloses nucleoside derivatives for the treatment of hepatitis C infection or EP679657, which discloses compounds that serve as ribonucleoside analogues or US2002058635, which discloses purine L-nucleoside compounds, in which both the purine rings and the sugar are either modified, functionalized, or both. So the sugar for example must show at least one esterified OH group.

WO06084281 discloses inhibitors of the E1 activation enzyme that have a sulfonamide moiety.
WO05051944 discloses oxetane-containing nucleosides, for the treatment of nucleoside analogue related disorders such as disorders involving cellular proliferation and infection.

WO9840384 discloses pyrazolopyrimidinones which are PDE1, 2 and 5 inhibitors and can be employed for the treatment of cardiovascular and cerebrovascular disorders and disorders of the urogenital system.
CH396 924, CH396 925, CH396 926, CH396 927, DE1147234, DE1149013, describe pyrazolopyrimidines which have a coronary-dilating effect and which can be employed for the treatment of disturbances of myocardial blood flow.
US3732225 describes pyrazolopyrimidines which have an anti-inflammatory and blood glucose-lowering effect.

DE2408906 describes styrylpyrazolopyrimidinones which can be employed as antimicrobial and anti-inflammatory agents for the treatment of, for example, oedema.

OBJECTIVE OF THE INVENTION

Changes in the substitution pattern of pyrazolopyrimidinones result in interesting changes concerning biological activity, respectively changes in the affinity towards different target enzymes.

Therefore it is an objective of the present invention to provide compounds as herein described, in particular in the claims, that effectively modulate PDE9A for the purpose of the development of a medicament, in particular in view of diseases or conditions, the treatment of which is accessible via PDE9A modulation.

It is another objective of the present invention to provide compounds that are useful for the manufacture of a medicament for the treatment of CNS disorders.

Yet another objective of the present invention is to provide compounds which show a favourable safety profile.

Another objective of the present invention is to provide compounds that have a favourable selectively profile in favour for PDE9A inhibition over other PDE family members and other pharmacological targets and by this may provide therapeutic advantage.

Yet another objective is to provide such a medicament that may not only serve for treatment but also for prevention or modification of the corresponding disease or condition.

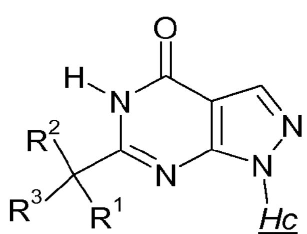
The present invention further provides a pharmaceutical composition comprising a compound as herein described, in particular in the claims, and a pharmaceutically acceptable carrier.

The present invention further provides a method of the treatment of any of the conditions as described herein in a mammal in need of such treatment, preferably a human, comprising administering to the mammal a therapeutically effective amount of a compound as herein described, in particular in the claims.

The present invention further provides a compound as herein described, in particular in the claims, for use in a method of treatment of the human or animal body by therapy.

DETAILED DESCRIPTION OF THE PRESENT INVENTION

The compounds of the present invention are characterised by general formula (I):



(I),

with the following definitions (substituents may be printed in bold for better reading):

Substituent ***Hc*** is defined by the following definitions **Hc**$^{\mathbf{i}}$, whereby the index i describes the order of preference, ascending from **Hc**$^{\mathbf{1}}$ to more preferably (i.e. **Hc**$^{\mathbf{2}}$), and so on:

Hc$^{\mathbf{1}}$:

Hc is tetrahydropyranyl-,

whereby one or more carbon ring atom(s) thereof optionally may be substituted by one or - where appropriate – by one or two substituents independently selected from

the group of fluorine, NC-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, C_{1-6}-alkyl-, C_{1-6}-alkyl-O- and up to one carbon ring atom may be substituted with oxo.

<u>Hc</u>^{2}:

<u>Hc</u> is 4-tetrahydropyranyl-,

whereby one or more carbon ring atom(s) thereof optionally may be substituted by one or - where appropriate – by one or two substituents independently selected from the group of fluorine, NC-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, C_{1-6}-alkyl-, C_{1-6}-alkyl-O- and up to one carbon ring atom may be substituted with oxo.

<u>Hc</u>^{3}:

<u>Hc</u> is unsubstituted 4-tetrahydropyranyl.

It will be evident that whenever *<u>Hc</u>* is tetrahydropyranyl – unsubstituted or not, it will be bound to the scaffold (factually to the nitrogen No. 1, see definition "scaffold" (=N1)) by one of the ring carbon atoms of said tetrahydropyranyl.

Substituent $\mathbf{R^1}$ is defined by the following definitions $\mathbf{R^{1.j}}$, respectively $\mathbf{R^{1.j}}$, whereby the index j describes the order of preference, ascending from $\mathbf{R^{1.1}}$ to more preferred definitions like $\mathbf{R^{1.2}}$, and so on:

$\mathbf{R^{1.1}}$:

$\mathbf{R^1}$ being the group

V—W—*

wherein

W is phenyl or heteroaryl;

V is phenyl or heteroaryl;

V preferably is attached at the 2 position of **W**, whereby the 1 position of **W** is the attachment point of **W** to the CR^2R^3 group in formula (I);

-* is the binding point by which **W** is attached to the CR^2R^3 group in formula (I);

wherein **W** and **V** independently of each other optionally may be substituted by one or more substituents selected from the group of fluorine, chlorine, bromine, C_{1-6}-alkyl-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, F_3C-O-, HF_2C-O-, C_{3-7}-heterocycloalkyl- (thereof preferably C_{3-5}-heterocycloalkyl-), H-O-C_{1-6}-alkyl-, C_{1-6}-alkyl-O-C_{1-6}-alkyl-, C_{3-7}-cycloalkyl-O-C_{1-6}-alkyl-, C_{3-7}-cycloalkyl-C_{1-3}-alkyl-O-C_{1-6}-alkyl-, phenyl-O-C_{1-6}-alkyl-, benzyl-O-C_{1-6}-alkyl-, H-O-, C_{1-6}-alkyl-O-, C_{3-7}-cycloalkyl-O-, C_{3-7}-cycloalkyl-C_{1-3}-alkyl-O-, phenyl-O-, benzyl-O-, N-morpholinyl, and NC-, preferably by a substituent selected from the group of fluorine, chlorine, bromine, C_{1-6}-alkyl-, F_3C-, F_3C-CH_2-, F_3C-O-, HF_2C-O-, C_{3-7}-heterocycloalkyl- (thereof preferably C_{3-5}-heterocycloalkyl-), C_{1-6}-alkyl-O-, C_{3-6}-cycloalkyl-O-, C_{3-6}-cycloalkyl-CH_2-O-, aryl-CH_2-O- and NC-.

$R^{1.2}$:

R^1 being the group

V—W—*

wherein

W is phenyl or a heteroaryl, the heteroaryl being selected from the group of oxadiazolyl, triazolyl, pyrazolyl, furanyl, pyridyl, pyrimidyl and pyridazinyl,

V is phenyl or heteroaryl, the heteroaryl being selected from the group of oxadiazolyl, triazolyl, pyrazolyl, pyrrolyl, furanyl, pyridyl, pyrimidyl and pyridazinyl,

V preferably is attached at the 2 position of **W**, whereby the 1 position of **W** is the attachment point of **W** to the CR^2R^3 group in formula (I);

-* is the binding point by which **W** is attached to the CR^2R^3 group in formula (I)

wherein **W** and **V** independently of each other optionally may be substituted by one or more substituents selected from the group of fluorine, chlorine, bromine, C_{1-6}-alkyl-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, F_3C-O-, HF_2C-O-, C_{3-7}-heterocycloalkyl- (thereof preferably C_{3-5}-heterocycloalkyl-), H-O-C_{1-6}-alkyl-, C_{1-6}-alkyl-O-C_{1-6}-alkyl-, C_{3-7}-cycloalkyl-O-C_{1-6}-alkyl-, C_{3-7}-cycloalkyl-C_{1-3}-alkyl-O-C_{1-6}-alkyl-, phenyl-O-C_{1-6}-alkyl-, benzyl-O-C_{1-6}-alkyl-, H-O-, C_{1-6}-alkyl-O-, C_{3-7}-cycloalkyl-O-, C_{3-7}-cycloalkyl-C_{1-3}-alkyl-O-, phenyl-O-, benzyl-O-, N-morpholinyl, and NC-, preferably by a substituent selected from the group of fluorine, chlorine, bromine, C_{1-6}-alkyl-, F_3C-, F_3C-CH_2-, F_3C-O-, HF_2C-O-, C_{3-7}-heterocycloalkyl- (thereof preferably C_{3-5}-heterocycloalkyl-), C_{1-6}-alkyl-O-, C_{3-6}-cycloalkyl-O-, C_{3-6}-cycloalkyl-CH_2-O-, aryl-CH_2-O- and NC-.

$R^{1.3}$:

R^1 being the group

V—W—*

wherein

W is phenyl or a heteroaryl, the heteroaryl being selected from the group of pyridyl, pyrimidyl and pyridazinyl,

V is phenyl or heteroaryl, the heteroaryl being selected from the group of oxadiazolyl, triazolyl, pyrazolyl, pyrrolyl, furanyl, pyridyl, pyrimidyl and pyridazinyl,

V preferably is attached at the 2 position of **W**, whereby the 1 position of **W** is the attachment point of **W** to the CR^2R^3 group in formula (I);

-* is the binding point by which **W** is attached to the CR^2R^3 group in formula (I)

wherein **W** and **V** independently of each other optionally may be substituted by one or more substituents selected from the group of fluorine, chlorine, bromine, C_{1-6}-alkyl-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, F_3C-O-, HF_2C-O-, C_{3-7}-heterocycloalkyl- (thereof preferably C_{3-5}-heterocycloalkyl-), H-O-C_{1-6}-alkyl-, C_{1-6}-alkyl-O-C_{1-6}-alkyl-, C_{3-7}-cycloalkyl-O-C_{1-6}-alkyl-, C_{3-7}-cycloalkyl-C_{1-3}-alkyl-O-C_{1-6}-alkyl-, phenyl-O-C_{1-6}-alkyl-, benzyl-O-C_{1-6}-alkyl-, H-O-, C_{1-6}-alkyl-O-, C_{3-7}-cycloalkyl-O-, C_{3-7}-cycloalkyl-C_{1-3}-alkyl-O-, phenyl-O-, benzyl-O-, N-morpholinyl, and NC-, preferably by a substituent selected from the group of fluorine, chlorine, bromine, C_{1-6}-alkyl-, F_3C-, F_3C-CH_2-, F_3C-O-, HF_2C-O-, C_{3-7}-heterocycloalkyl- (thereof preferably C_{3-5}-heterocycloalkyl-), C_{1-6}-alkyl-O-, C_{3-6}-cycloalkyl-O-, C_{3-6}-cycloalkyl-CH_2-O-, aryl-CH_2-O- and NC-.

$R^{1.4}$:

R^1 being the group

V—W—*

wherein

W is phenyl or pyridinyl,

V is phenyl or heteroaryl, the heteroaryl being selected from the group of oxadiazolyl, triazolyl, pyrazolyl, furanyl, pyridyl, pyrimidyl and pyridazinyl,

V preferably is attached at the 2 position of **W**, whereby the 1 position of **W** is the attachment point of **W** to the CR^2R^3 group in formula (I);

-* is the binding point by which **W** is attached to the CR^2R^3 group in formula (I)

wherein **W** and **V** independently of each other optionally may be substituted by one or more substituents selected from the group of fluorine, chlorine, bromine, C_{1-6}-alkyl-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, F_3C-O-, HF_2C-O-, C_{3-7}-heterocycloalkyl- (thereof preferably C_{3-5}-heterocycloalkyl-), H-O-C_{1-6}-alkyl-, C_{1-6}-alkyl-O-C_{1-6}-alkyl-, C_{3-7}-cycloalkyl-O-C_{1-6}-alkyl-, C_{3-7}-cycloalkyl-C_{1-3}-alkyl-O-C_{1-6}-alkyl-, phenyl-O-C_{1-6}-alkyl-, benzyl-O-C_{1-6}-alkyl-, H-O-, C_{1-6}-alkyl-O-, C_{3-7}-cycloalkyl-O-, C_{3-7}-cycloalkyl-C_{1-3}-alkyl-O-, phenyl-O-, benzyl-O-, N-morpholinyl, and NC-, preferably by a substituent selected from the group of fluorine, chlorine, bromine, C_{1-6}-alkyl-, F_3C-, F_3C-CH_2-, F_3C-O-, HF_2C-O-, C_{3-7}-heterocycloalkyl- (thereof preferably C_{3-5}-heterocycloalkyl-), C_{1-6}-alkyl-O-, C_{3-6}-cycloalkyl-O-, C_{3-6}-cycloalkyl-CH_2-O-, aryl-CH_2-O- and NC-,

wherein more preferably **W** and **V** independently of each other optionally may be substituted by one or more substituents selected from the group of fluorine, chlorine, H_3C-, F_3C-, CH_3O-, N-morpholinyl, and NC-, more preferably selected from the group of fluorine, H_3C-, F_3C-, CH_3O- and NC-;

$R^{1.5}$:

R^1 being the group

V—W—*

wherein

W is phenyl or pyridyl,

V is phenyl or heteroaryl, the heteroaryl being selected from the group of oxadiazolyl, triazolyl, pyrazolyl, pyrrolyl, furanyl, pyridyl, pyrimidyl and pyridazinyl,

V preferably is attached at the 2 position of **W**, whereby the 1 position of **W** is the attachment point of **W** to the CR^2R^3 group in formula (I);

-* is the binding point by which **W** is attached to the CR^2R^3 group in formula (I);

wherein **W** optionally may be substituted by one or more substituents selected from the group of fluorine, chlorine, bromine, H_3C-, F_3C-, CH_3O- and NC-, preferably selected from the group of fluorine, chlorine and F_3C-;

and wherein **V** optionally may be substituted by one or more substituents selected from the group of fluorine, chlorine, H_3C-, *tert*-butyl-, F_3C-, CH_3O-, cyclobutyloxy-, N-morpholinyl, benzyl-O- and NC-.

$R^{1.6}$:

R^1 being the group

V—W—*

wherein

W is phenyl whereby **W** optionally is substituted by a fluorine, chlorine or F_3C-;

V is heteroaryl being selected from the group of oxadiazolyl, triazolyl, pyrazolyl, pyrrolyl, furanyl, pyridyl, pyrimidyl and pyridazinyl, whereby

V optionally is substituted by 1 to 4, preferably 1 or 2, more preferably 1 substituent independently of each other selected from the group of fluorine, chlorine, H_3C-, *tert*-butyl-, F_3C-, CH_3O-, cyclobutyloxy-, N-morpholinyl, benzyl-O- and NC-,

V is attached at the 2 position of **W**, whereby the 1 position of **W** is the attachment point of **W** to the CR^2R^3 group in formula (I);

-* is the binding point by which **W** is attached to the CR^2R^3 group in formula (I)

For each definition of $\mathbf{R^1}$ (i.e. $\mathbf{R^{1.1}}$, $\mathbf{R^{1.2}}$, $\mathbf{R^{1.3}}$, $\mathbf{R^{1.4}}$, $\mathbf{R^{1.5}}$, $\mathbf{R^{1.6}}$):

- whenever **V** may be oxadiazolyl, the preferred isomer is 1,2,4-oxadiazol-3-yl;
- whenever **V** may be triazolyl, the preferred isomer is 1,2,4-trizaol-1-yl;
- whenever **V** may be pyrazolyl, it is preferably pyrazol-1-yl or pyrazol-4-yl;
- whenever **V** may be furanyl, it is preferably furan-2-yl;
- whenever **V** may be pyridyl, preferably it may be 2-, 3- or 4-pyridyl, more preferably pyridin-2-yl;
- whenever **V** may be pyrimidinyl, preferably it may be 5- pyrimidinyl;
- whenever **V** may be pyridazinyl, preferably it may be 3- or 4- pyridazinyl.

$\mathbf{R^2}$:

$\mathbf{R^2}$ being selected from the group of H-, fluorine, F_3C-, HF_2C-, FH_2C-, and C_{1-3}-alkyl-, preferably $\mathbf{R^2}$ being H.

$\mathbf{R^3}$:

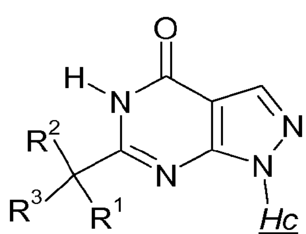
$\mathbf{R^3}$ being selected from the group of H-, fluorine, F_3C-, HF_2C-, FH_2C-, and C_{1-3}-alkyl-, preferably $\mathbf{R^3}$ being H.

Potential isoforms, tautomers, stereoisomers, solvates, hydrates, and/or the addition salts of any compound according to the invention, particularly the physiologically acceptable salts thereof with inorganic or organic acids or bases, or the combinations thereof are subject of the present invention as well.

Individual generic (genius) embodiments of compounds according to formula (I) are defined by the group of **<u>Hc</u>**$^{\mathbf{i}}$, $\mathbf{R}^{\mathbf{1.j}}$ and $\mathbf{R}^{\mathbf{2}}$ and $\mathbf{R}^{\mathbf{3}}$ as described above. So given the above definitions, preferred individual compound embodiments of the invention are fully characterised by the term (**<u>Hc</u>**$^{\mathbf{i}}$, $\mathbf{R}^{\mathbf{1.j}}$) if $\mathbf{R}^{\mathbf{2}}$ and $\mathbf{R}^{\mathbf{3}}$ are as defined above and if for each letter i and j an individual figure is given. Indices vary independently from each other.

The following matrix table (Table 1) shows, exemplary and in the order of increasing preference from the first line to the last line, such embodiments E-1 to E-24 of the invention that are considered preferred. This means that embodiment E-24, represented by the entries in the last row of table 1 is the most preferred embodiment:

Table 1: *Preferred generic (genius) embodiments E-1 to E-24 of the invention: Compounds of the present invention are characterised by general formula (I):*



(I),

with

	<u>Hc</u>	$\mathbf{R^1}$	$\mathbf{R^2}$	$\mathbf{R^3}$
E-1	<u>Hc</u>^{1}	$R^{1.1}$	defined by footnote[1)]	defined by footnote[2)]
E-2	<u>Hc</u>^{1}	$R^{1.2}$	defined by footnote[1)]	defined by footnote[2)]
E-3	<u>Hc</u>^{1}	$R^{1.3}$	defined by footnote[1)]	defined by footnote[2)]
E-4	<u>Hc</u>^{1}	$R^{1.4}$	defined by footnote[1)]	defined by footnote[2)]

E-5	$\underline{Hc}^{1}$	$R^{1.5}$	defined by footnote1)	defined by footnote2)
E-6	$\underline{Hc}^{1}$	$R^{1.6}$	defined by footnote1)	defined by footnote2)
E-7	$\underline{Hc}^{1}$	$R^{1.5}$	being H	being H
E-8	$\underline{Hc}^{1}$	$R^{1.6}$	being H	being H

E-9	$\underline{Hc}^{2}$	$R^{1.1}$	defined by footnote1)	defined by footnote2)
E-10	$\underline{Hc}^{2}$	$R^{1.2}$	defined by footnote1)	defined by footnote2)
E-11	$\underline{Hc}^{2}$	$R^{1.3}$	defined by footnote1)	defined by footnote2)
E-12	$\underline{Hc}^{2}$	$R^{1.4}$	defined by footnote1)	defined by footnote2)
E-13	$\underline{Hc}^{2}$	$R^{1.5}$	defined by footnote1)	defined by footnote2)
E-14	$\underline{Hc}^{2}$	$R^{1.6}$	defined by footnote1)	defined by footnote2)
E-15	$\underline{Hc}^{2}$	$R^{1.5}$	being H	being H
E-16	$\underline{Hc}^{2}$	$R^{1.6}$	being H	being H

E-17	$\underline{Hc}^{3}$	$R^{1.1}$	defined by footnote1)	defined by footnote2)
E-18	$\underline{Hc}^{3}$	$R^{1.2}$	defined by footnote1)	defined by footnote2)
E-19	$\underline{Hc}^{3}$	$R^{1.3}$	defined by footnote1)	defined by footnote2)
E-20	$\underline{Hc}^{3}$	$R^{1.4}$	defined by footnote1)	defined by footnote2)
E-21	$\underline{Hc}^{3}$	$R^{1.5}$	defined by footnote1)	defined by footnote2)
E-22	$\underline{Hc}^{3}$	$R^{1.6}$	defined by footnote1)	defined by footnote2)
E-23	$\underline{Hc}^{3}$	$R^{1.5}$	being H	being H
E-24	$\underline{Hc}^{3}$	$R^{1.6}$	being H	being H

Footnotes:

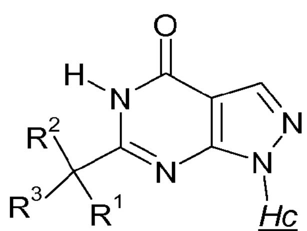
1) the definition refers to: **R^2** being selected from the group of H-, fluorine, F_3C-, HF_2C-, FH_2C-, and C_{1-3}-alkyl-, preferably **R^2** being H.

2) the definition refers to: **R^3** being selected from the group of H-, fluorine, F_3C-, HF_2C-, FH_2C-, and C_{1-3}-alkyl-, preferably **R^3** being H.

In all these embodiments of table 1 it is preferred that each of **R^2** and **R^3** is H.

Where appropriate, the subject matter of the invention also refers to the isoforms, tautomers, stereoisomers, solvates, hydrates, and the salts of any compound, particularly the physiologically acceptable salts thereof with suited inorganic or organic acids or bases, or the combinations thereof.

One such embodiment according to the invention concerns a compound according to general formula (I)



(I),

with

<u>Hc</u> being tetrahydropyranyl-, preferably 4-tetrahydropyranyl,

whereby one or more carbon ring atom(s) thereof optionally may be substituted by one or - where appropriate - by two substituents independently selected from the group of fluorine, NC-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, C_{1-6}-alkyl-, C_{1-6}-alkyl-O- and up to one carbon ring atom may be substituted with oxo;

R^1 being the group

V—W—* , wherein

W is selected from the group of phenyl or heteroaryl;

V is selected from the group of phenyl or heteroaryl;

V preferably is attached at the 2 position of **W**, whereby the 1 position of **W** is the attachment point of **W** to the CR^2R^3 group in formula (I);

-* is the binding point by which **W** is attached to the CR^2R^3 group in formula (I);

wherein **W** and **V** independently of each other optionally may be substituted by one or more substituents selected from the group of fluorine, chlorine, bromine, C_{1-6}-alkyl-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, F_3C-O-, HF_2C-O-, C_{3-7}-heterocycloalkyl- (thereof preferably C_{3-5}-heterocycloalkyl-), H-O-C_{1-6}-alkyl-, C_{1-6}-alkyl-O-C_{1-6}-alkyl-, C_{3-7}-cycloalkyl-O-C_{1-6}-alkyl-, C_{3-7}-cycloalkyl-C_{1-3}-alkyl-O-C_{1-6}-alkyl-, phenyl-O-C_{1-6}-alkyl-, benzyl-O-C_{1-6}-alkyl-, H-O-, C_{1-6}-alkyl-O-, C_{3-7}-cycloalkyl-O-, C_{3-7}-cycloalkyl-C_{1-3}-alkyl-O-, phenyl-O-, benzyl-O-, N-morpholinyl, and NC-, preferably by a substituent selected from the group of fluorine, chlorine, bromine, C_{1-6}-alkyl-, F_3C-, F_3C-CH_2-, F_3C-O-, HF_2C-O-, C_{3-7}-heterocycloalkyl- (thereof preferably C_{3-5}-heterocycloalkyl-), C_{1-6}-alkyl-O-, C_{3-6}-cycloalkyl-O-, C_{3-6}-cycloalkyl-CH_2-O-, aryl-CH_2-O- and NC-;

$\mathbf{R^2}$ being selected from the group of H-, fluorine, F_3C-, HF_2C-, FH_2C-, and C_{1-3}-alkyl-, preferably $\mathbf{R^2}$ being H;

$\mathbf{R^3}$ being selected from the group of H-, fluorine, F_3C-, HF_2C-, FH_2C-, and C_{1-3}-alkyl-, preferably $\mathbf{R^3}$ being H;

and the salts thereof, preferably pharmaceutically acceptable salts thereof.

In another embodiment the compounds of the invention are compounds according to general formula (I), with

Hc being tetrahydropyranyl-, preferably 4-tetrahydropyranyl,

whereby one or more carbon ring atom(s) thereof optionally may be substituted by one or - where appropriate – by one or two substituents independently selected from the group of fluorine, NC-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, C_{1-6}-alkyl-, C_{1-6}-alkyl-O- and up to one carbon ring atom may be substituted with oxo;

$\mathbf{R^1}$ being the group

V—W—* , wherein

W is selected from the group of phenyl or a heteroaryl, the heteroaryl being selected from the group of oxadiazolyl, triazolyl, pyrazolyl, furanyl, pyridyl, pyrimidyl and pyridazinyl,

V is selected from the group of phenyl or heteroaryl, the heteroaryl being selected from the group of oxadiazolyl, triazolyl, pyrazolyl, pyrrolyl, furanyl, pyridyl, pyrimidyl and pyridazinyl,

V preferably is attached at the 2 position of **W**, whereby the 1 position of **W** is the attachment point of **W** to the CR^2R^3 group in formula (I);

wherein **W** and **V** independently of each other optionally may be substituted by one or more substituents selected from the group of fluorine, chlorine, bromine, C_{1-6}-alkyl-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, F_3C-O-, HF_2C-O-, C_{3-7}-heterocycloalkyl- (thereof preferably C_{3-5}-heterocycloalkyl-), H-O-C_{1-6}-alkyl-, C_{1-6}-alkyl-O-C_{1-6}-alkyl-, C_{3-7}-cycloalkyl-O-C_{1-6}-alkyl-, C_{3-7}-cycloalkyl-C_{1-3}-alkyl-O-C_{1-6}-alkyl-, phenyl-O-C_{1-6}-alkyl-, benzyl-O-C_{1-6}-alkyl-, H-O-, C_{1-6}-alkyl-O-, C_{3-7}-cycloalkyl-O-, C_{3-7}-cycloalkyl-C_{1-3}-alkyl-O-, phenyl-O-, benzyl-O-, N-morpholinyl, and NC-, preferably by a substituent selected from the group of fluorine, chlorine, bromine, C_{1-6}-alkyl-, F_3C-, F_3C-CH_2-, F_3C-O-, HF_2C-O-, C_{3-7}-heterocycloalkyl- (thereof preferably C_{3-5}-heterocycloalkyl-), C_{1-6}-alkyl-O-, C_{3-6}-cycloalkyl-O-, C_{3-6}-cycloalkyl-CH_2-O-, aryl-CH_2-O- and NC-;

R^2 being selected from the group of H-, fluorine, F_3C-, HF_2C-, FH_2C-, and C_{1-3}-alkyl-, preferably **R^2** being H;

R^3 being selected from the group of H-, fluorine, F_3C-, HF_2C-, FH_2C-, and C_{1-3}-alkyl-, preferably **R^3** being H;

and the salts thereof, preferably pharmaceutically acceptable salts thereof.

In another embodiment the compounds of the invention are compounds according to general formula (I), with

Hc being tetrahydropyranyl-,

whereby one or more carbon ring atom(s) thereof optionally may be substituted by one or - where appropriate – by one or two substituents independently selected from the group of fluorine, NC-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, C_{1-6}-alkyl-, C_{1-6}-alkyl-O- and up to one carbon ring atom may be substituted with oxo;

R^1 being the group

V—W—* , wherein

W is selected from the group of phenyl or a heteroaryl, the heteroaryl being selected from the group of pyridyl, pyrimidyl and pyridazinyl,

V is selected from the group of phenyl or heteroaryl, the heteroaryl being selected from the group of oxadiazolyl, triazolyl, pyrazolyl, pyrrolyl, furanyl, pyridyl, pyrimidyl and pyridazinyl,

V preferably is attached at the 2 position of **W**, whereby the 1 position of **W** is the attachment point of **W** to the CR^2R^3 group in formula (I);

wherein **W** and **V** independently of each other optionally may be substituted by one or more substituents selected from the group of fluorine, chlorine, bromine, C_{1-6}-alkyl-

, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, F_3C-O-, HF_2C-O-, C_{3-7}-heterocycloalkyl- (thereof preferably C_{3-5}-heterocycloalkyl-), H-O-C_{1-6}-alkyl-, C_{1-6}-alkyl-O-C_{1-6}-alkyl-, C_{3-7}-cycloalkyl-O-C_{1-6}-alkyl-, C_{3-7}-cycloalkyl-C_{1-3}-alkyl-O-C_{1-6}-alkyl-, phenyl-O-C_{1-6}-alkyl-, benzyl-O-C_{1-6}-alkyl-, H-O-, C_{1-6}-alkyl-O-, C_{3-7}-cycloalkyl-O-, C_{3-7}-cycloalkyl-C_{1-3}-alkyl-O-, phenyl-O-, benzyl-O-, N-morpholinyl, and NC-, preferably by a substituent selected from the group of fluorine, chlorine, bromine, C_{1-6}-alkyl-, F_3C-, F_3C-CH_2-, F_3C-O-, HF_2C-O-, C_{3-7}-heterocycloalkyl- (thereof preferably C_{3-5}-heterocycloalkyl-), C_{1-6}-alkyl-O-, C_{3-6}-cycloalkyl-O-, C_{3-6}-cycloalkyl-CH_2-O-, aryl-CH_2-O- and NC-;

$\mathbf{R^2}$ being selected from the group of H-, fluorine, F_3C-, HF_2C-, FH_2C-, and C_{1-3}-alkyl-, preferably $\mathbf{R^2}$ being H;

$\mathbf{R^3}$ being selected from the group of H-, fluorine, F_3C-, HF_2C-, FH_2C-, and C_{1-3}-alkyl-, preferably $\mathbf{R^3}$ being H;

and the salts thereof, preferably pharmaceutically acceptable salts thereof.

In another embodiment the compounds of the invention are compounds according to general formula (I), with

Hc being tetrahydropyranyl-,

whereby one or more carbon ring atom(s) thereof optionally may be substituted by one or - where appropriate – by one or two substituents independently selected from the group of fluorine, NC-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, C_{1-6}-alkyl-, C_{1-6}-alkyl-O- and up to one carbon ring atom may be substituted with oxo;

$\mathbf{R^1}$ being the group

$V-W-*$, wherein

W is selected from the group of phenyl or pyridinyl,

V is selected from the group of phenyl or heteroaryl, the heteroaryl being selected from the group of oxadiazolyl, triazolyl, pyrazolyl, furanyl, pyridyl, pyrimidyl and pyridazinyl,

V preferably is attached at the 2 position of **W**, whereby the 1 position of **W** is the attachment point of **W** to the CR^2R^3 group in formula (I);

wherein **W** and **V** independently of each other optionally may be substituted by one or more substituents selected from the group of fluorine, chlorine, bromine, C_{1-6}-alkyl-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, F_3C-O-, HF_2C-O-, C_{3-7}-heterocycloalkyl- (thereof preferably C_{3-5}-heterocycloalkyl-), H-O-C_{1-6}-alkyl-, C_{1-6}-alkyl-O-C_{1-6}-alkyl-, C_{3-7}-cycloalkyl-O-C_{1-6}-alkyl-, C_{3-7}-cycloalkyl-C_{1-3}-alkyl-O-C_{1-6}-alkyl-, phenyl-O-C_{1-6}-alkyl-, benzyl-O-C_{1-6}-alkyl-, H-O-, C_{1-6}-alkyl-O-, C_{3-7}-cycloalkyl-O-, C_{3-7}-cycloalkyl-C_{1-3}-alkyl-O-, phenyl-O-, benzyl-O-, N-morpholinyl, and NC-, preferably by a substituent selected from the group of fluorine, chlorine, bromine, C_{1-6}-alkyl-, F_3C-, F_3C-CH_2-, F_3C-O-, HF_2C-O-, C_{3-7}-heterocycloalkyl- (thereof preferably C_{3-5}-heterocycloalkyl-), C_{1-6}-alkyl-O-, C_{3-6}-cycloalkyl-O-, C_{3-6}-cycloalkyl-CH_2-O-, aryl-CH_2-O- and NC-,

wherein preferably **W** and **V** independently of each other optionally may be substituted by one or more substituents selected from the group of fluorine, chlorine, H_3C-, F_3C-, CH_3O-, N-morpholinyl, and NC-, preferably selected from the group of fluorine, H_3C-, F_3C-, CH_3O- and NC-;

$\mathbf{R^2}$ being selected from the group of H-, fluorine, F_3C-, HF_2C-, FH_2C-, and C_{1-3}-alkyl-, preferably $\mathbf{R^2}$ being H;

$\mathbf{R^3}$ being selected from the group of H-, fluorine, F_3C-, HF_2C-, FH_2C-, and C_{1-3}-alkyl-, preferably $\mathbf{R^3}$ being H;

and the salts thereof, preferably pharmaceutically acceptable salts thereof.

In another embodiment the compounds of the invention are compounds according to general formula (I), with

<u>Hc</u> being tetrahydropyranyl-,

whereby one or more carbon ring atom(s) thereof optionally may be substituted by one or - where appropriate – by one or two substituents independently selected from the group of fluorine, NC-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, C_{1-6}-alkyl-, C_{1-6}-alkyl-O- and up to one carbon ring atom may be substituted with oxo;

$\mathbf{R^1}$ being the group

V—W—* , wherein

W is selected from the group of phenyl or pyridyl,

V is selected from the group of phenyl or heteroaryl, the heteroaryl being selected from the group of oxadiazolyl, triazolyl, pyrazolyl, pyrrolyl, furanyl, pyridyl, pyrimidyl and pyridazinyl,

V preferably is attached at the 2 position of **W**, whereby the 1 position of **W** is the attachment point of **W** to the CR^2R^3 group in formula (I);

wherein **W** optionally may be substituted by one or more substituents selected from the group of fluorine, chlorine, bromine, H_3C-, F_3C-, CH_3O- and NC-, preferably selected from the group of fluorine, chlorine and F_3C-;

and wherein **V** optionally may be substituted by one or more substituents selected from the group of fluorine, chlorine, H_3C-, tert-butyl-, F_3C-, CH_3O-, cyclobutyloxy-, N-morpholinyl, benzyl-O- and NC-;

$\mathbf{R^2}$ being selected from the group of H-, fluorine, F_3C-, HF_2C-, FH_2C-, and C_{1-3}-alkyl-, preferably $\mathbf{R^2}$ being H;

R^3 being selected from the group of H-, fluorine, F_3C-, HF_2C-, FH_2C-, and C_{1-3}-alkyl-, preferably **R^3** being H;

and the salts thereof, preferably pharmaceutically acceptable salts thereof.

In another embodiment the compounds of the invention are compounds according to general formula (I), with

Hc being tetrahydropyranyl-,

whereby one or more carbon ring atom(s) thereof optionally may be substituted by one or - where appropriate – by one or two substituents independently selected from the group of fluorine, NC-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, C_{1-6}-alkyl-, C_{1-6}-alkyl-O- and up to one carbon ring atom may be substituted with oxo;

R^1 being the group

V—W—* , wherein

W is phenyl whereby **W** optionally is substituted by a fluorine, chlorine or F_3C-;

V is heteroaryl being selected from the group of oxadiazolyl, triazolyl, pyrazolyl, pyrrolyl, furanyl, pyridyl, pyrimidyl and pyridazinyl, whereby

V optionally is substituted by 1 to 4, preferably 1 or 2, more preferably 1 substituent independently of each other selected from the group of fluorine, chlorine, H_3C-, *tert*-butyl-, F_3C-, CH_3O-, cyclobutyloxy-, N-morpholinyl, benzyl-O- and NC-,

V is attached at the 2 position of **W**, whereby the 1 position of **W** is the attachment point of **W** to the CR^2R^3 group in formula (I);

R^2 being selected from the group of H-, fluorine, F_3C-, HF_2C-, FH_2C-, and C_{1-3}-alkyl-, preferably **R^2** being H;

R^3 being selected from the group of H-, fluorine, F_3C-, HF_2C-, FH_2C-, and C_{1-3}-alkyl-, preferably **R**^{3} being H;

and the salts thereof, preferably pharmaceutically acceptable salts thereof.

In another embodiment the compounds of the invention are compounds according to general formula (I), with

__Hc__ being 4-tetrahydropyranyl-,

whereby each carbon ring atom thereof optionally may be substituted by one or - where appropriate – by one or two substituents independently selected from the group of fluorine, NC-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, C_{1-6}-alkyl-, C_{1-6}-alkyl-O- and up to one carbon ring atom may be substituted with oxo,

preferably ***__Hc__*** being unsubstituted 4-tetrahydropyranyl-;

R^1 being the group

V—W—* , wherein

W is selected from the group of phenyl or pyridinyl,

V is selected from the group of phenyl or heteroaryl, the heteroaryl being selected from the group of oxadiazolyl, triazolyl, pyrazolyl, furanyl, pyridyl, pyrimidyl and pyridazinyl,

V preferably is attached at the 2 position of **W**, whereby the 1 position of **W** is the attachment point of **W** to the CR^2R^3 group in formula (I);

wherein **W** and **V** independently of each other optionally may be substituted by one or more substituents selected from the group of fluorine, chlorine, bromine, C_{1-6}-alkyl-

, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, F_3C-O-, HF_2C-O-, C_{3-7}-heterocycloalkyl- (thereof preferably C_{3-5}-heterocycloalkyl-), H-O-C_{1-6}-alkyl-, C_{1-6}-alkyl-O-C_{1-6}-alkyl-, C_{3-7}-cycloalkyl-O-C_{1-6}-alkyl-, C_{3-7}-cycloalkyl-C_{1-3}-alkyl-O-C_{1-6}-alkyl-, phenyl-O-C_{1-6}-alkyl-, benzyl-O-C_{1-6}-alkyl-, H-O-, C_{1-6}-alkyl-O-, C_{3-7}-cycloalkyl-O-, C_{3-7}-cycloalkyl-C_{1-3}-alkyl-O-, phenyl-O-, benzyl-O-, N-morpholinyl, and NC-, preferably by a substituent selected from the group of fluorine, chlorine, bromine, C_{1-6}-alkyl-, F_3C-, F_3C-CH_2-, F_3C-O-, HF_2C-O-, C_{3-7}-heterocycloalkyl- (thereof preferably C_{3-5}-heterocycloalkyl-), C_{1-6}-alkyl-O-, C_{3-6}-cycloalkyl-O-, C_{3-6}-cycloalkyl-CH_2-O-, aryl-CH_2-O- and NC-,

wherein more preferably **W** and **V** independently of each other optionally may be substituted by one or more substituents selected from the group of fluorine, chlorine, H_3C-, F_3C-, CH_3O-, N-morpholinyl, and NC-, more preferably selected from the group of fluorine, H_3C-, F_3C-, CH_3O- and NC-;

$\mathbf{R^2}$ being selected from the group of H-, fluorine, F_3C-, HF_2C-, FH_2C-, and C_{1-3}-alkyl-, preferably $\mathbf{R^2}$ being H;

$\mathbf{R^3}$ being selected from the group of H-, fluorine, F_3C-, HF_2C-, FH_2C-, and C_{1-3}-alkyl-, preferably $\mathbf{R^3}$ being H;

and the salts thereof, preferably pharmaceutically acceptable salts thereof.

In another embodiment the compounds of the invention are compounds according to general formula (I), with

Hc being 4-tetrahydropyranyl-,

whereby each carbon ring atom thereof optionally may be substituted by one or - where appropriate – by one or two substituents independently selected from the group of fluorine, NC-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, C_{1-6}-alkyl-, C_{1-6}-alkyl-O- and up to one carbon ring atom may be substituted with oxo,

preferably ***Hc*** being unsubstituted 4-tetrahydropyranyl-;

R^1 being the group

$$V{-}W{-}*$$, wherein

W is selected from the group of phenyl or pyridyl,

V is selected from the group of phenyl or heteroaryl, the heteroaryl being selected from the group of oxadiazolyl, triazolyl, pyrazolyl, pyrrolyl, furanyl, pyridyl, pyrimidyl and pyridazinyl,

V preferably is attached at the 2 position of **W**, whereby the 1 position of **W** is the attachment point of **W** to the CR^2R^3 group in formula (I);

wherein **W** optionally may be substituted by one or more substituents selected from the group of fluorine, chlorine, bromine, H_3C-, F_3C-, CH_3O- and NC-, preferably selected from the group of fluorine, chlorine and F_3C-;

and wherein **V** optionally may be substituted by one or more substituents selected from the group of fluorine, chlorine, H_3C-, *tert*-butyl-, F_3C-, CH_3O-, cyclobutyloxy-, N-morpholinyl, benzyl-O- and NC-;

R^2 being selected from the group of H-, fluorine, F_3C-, HF_2C-, FH_2C-, and C_{1-3}-alkyl-, preferably **R^2** being H;

R^3 being selected from the group of H-, fluorine, F_3C-, HF_2C-, FH_2C-, and C_{1-3}-alkyl-, preferably **R^3** being H;

and the salts thereof, preferably pharmaceutically acceptable salts thereof.

In another embodiment the compounds of the invention are compounds according to general formula (I), with

Hc being 4-tetrahydropyranyl-,

whereby each carbon ring atom thereof optionally may be substituted by one or - where appropriate – by one or two substituents independently selected from the group of fluorine, NC-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, C_{1-6}-alkyl-, C_{1-6}-alkyl-O- and up to one carbon ring atom may be substituted with oxo,

preferably ***Hc*** being unsubstituted 4-tetrahydropyranyl-;

R^1 being the group

V—W—* , wherein

W is phenyl whereby **W** optionally is substituted by a fluorine, chlorine or F_3C-;

V is heteroaryl being selected from the group of oxadiazolyl, triazolyl, pyrazolyl, pyrrolyl, furanyl, pyridyl, pyrimidyl and pyridazinyl, whereby

V optionally is substituted by 1 to 4, preferably 1 or 2, more preferably 1 substituent independently of each other selected from the group of fluorine, chlorine, H_3C-, *tert*-butyl-, F_3C-, CH_3O-, cyclobutyloxy-, N-morpholinyl, benzyl-O- and NC-,

V is attached at the 2 position of **W**, whereby the 1 position of **W** is the attachment point of **W** to the CR^2R^3 group in formula (I);

R^2 being selected from the group of H-, fluorine, F_3C-, HF_2C-, FH_2C-, and C_{1-3}-alkyl-, preferably **R^2** being H;

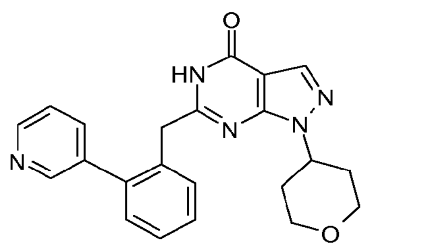
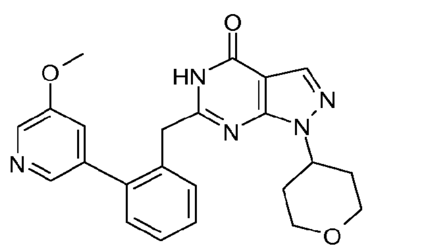
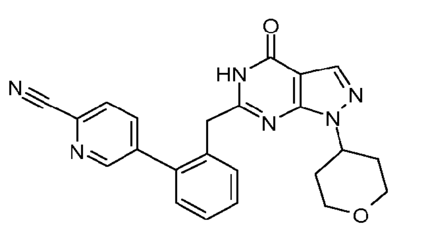
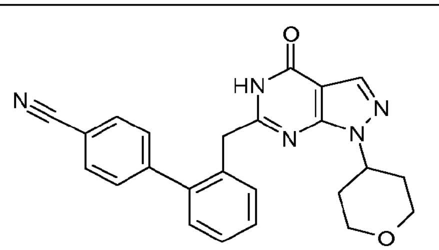
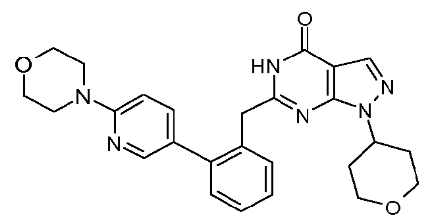
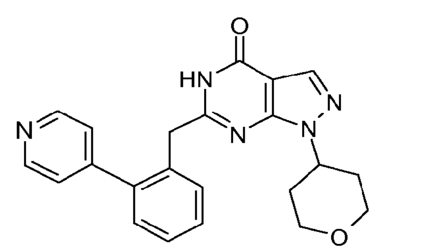
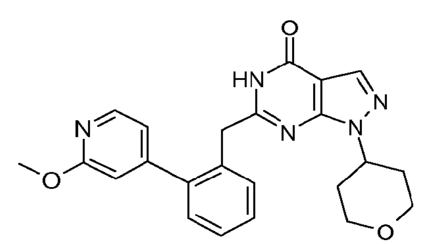
R^3 being selected from the group of H-, fluorine, F_3C-, HF_2C-, FH_2C-, and C_{1-3}-alkyl-, preferably **R^3** being H;

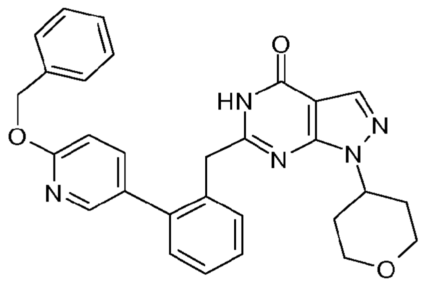
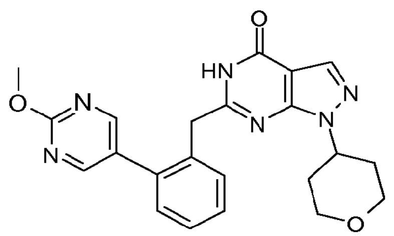
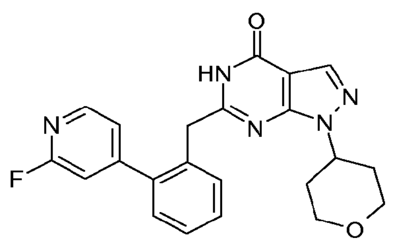
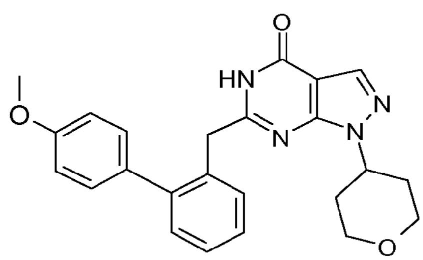
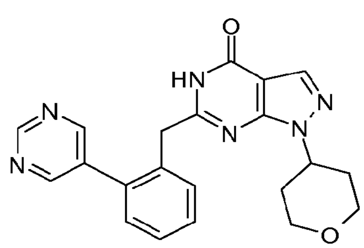
and the salts thereof, preferably pharmaceutically acceptable salts thereof.

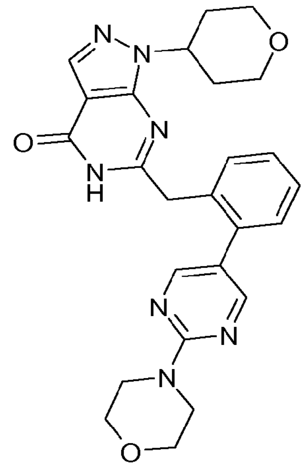
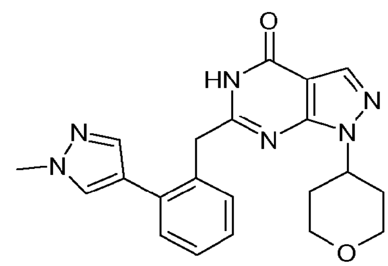
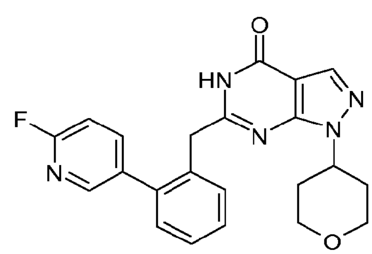
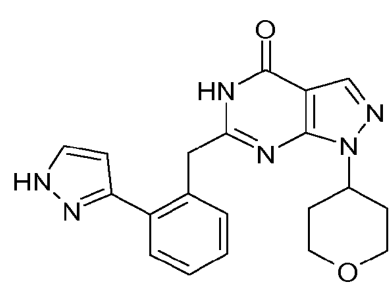
<u>Specifically preferred compounds</u>

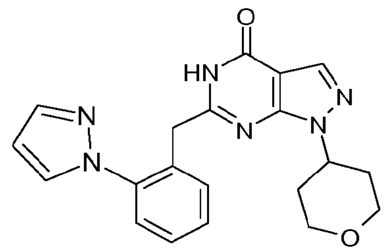
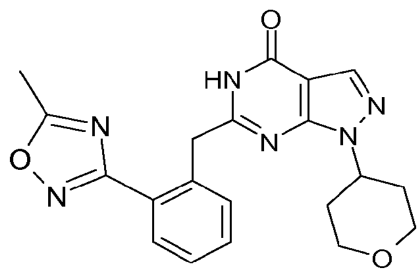
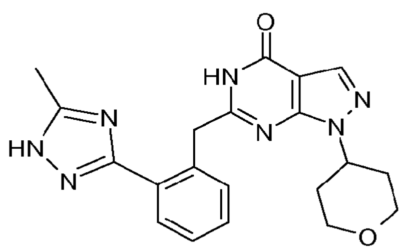
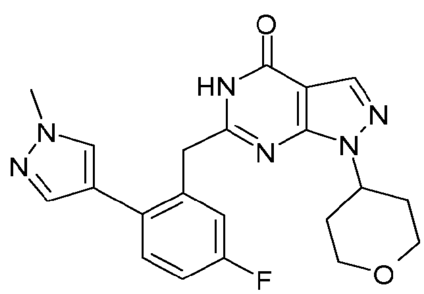
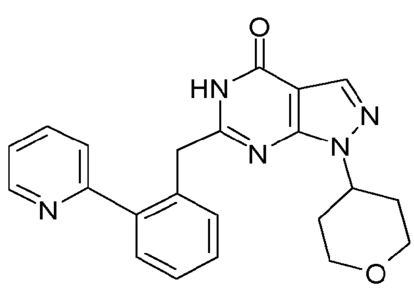
Each of the compounds presented in the following table (Table 2) is specifically and individually preferred according to the invention. The listed compounds are described in detail in the section “**Exemplary embodiments**”. The following list presents the specific compounds of the invention as “neutral” compounds, i.e. not in form of salts and the like. The example numbers correspond with the numbering according to the section “Exemplary embodiments”. More specific information can be found in the section “Exemplary embodiments”.

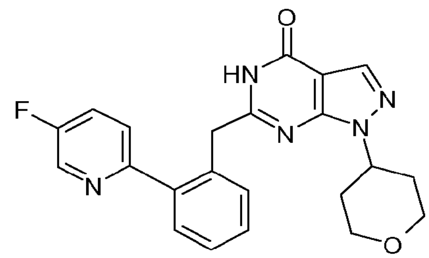
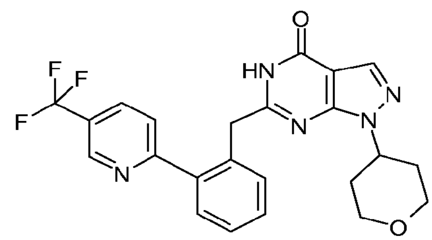
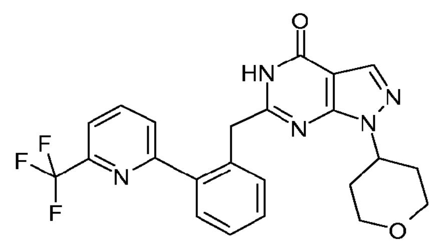
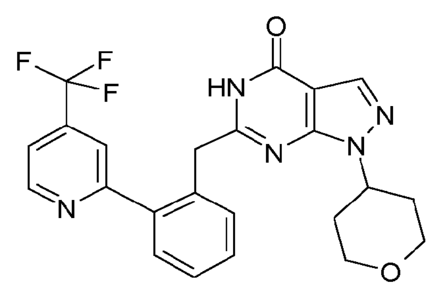
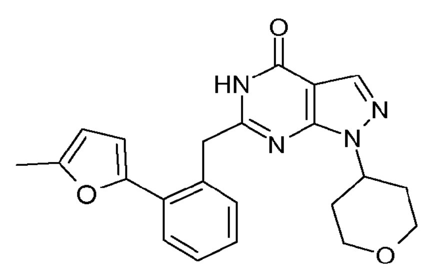
Table 2: *preferred specific embodiments. The reference numbers correspond with the ones used in the experimental part. The first column refers to the example number / reference number respectively, the second column to the structure.*

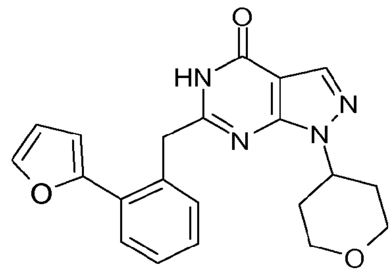
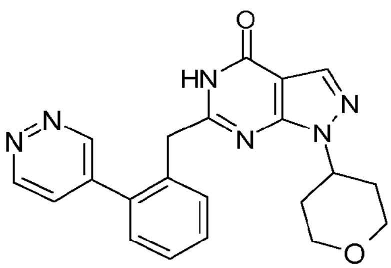
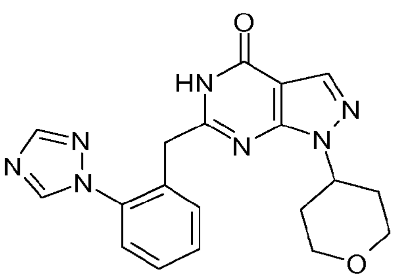
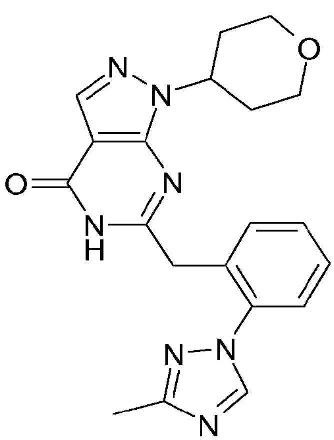
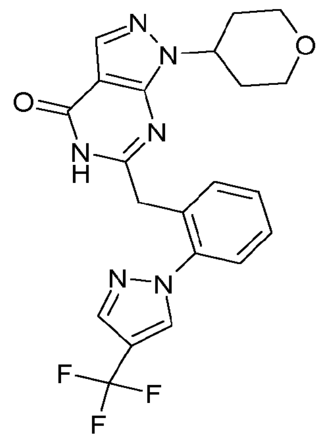
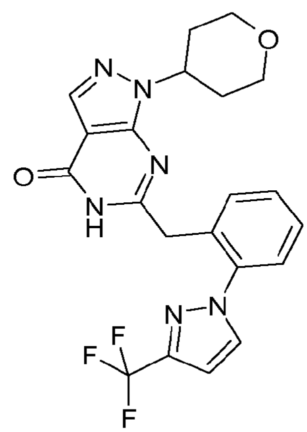
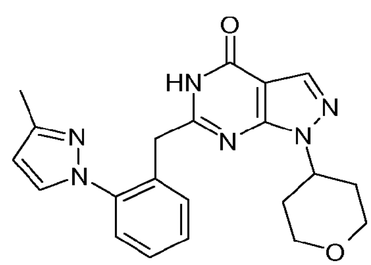
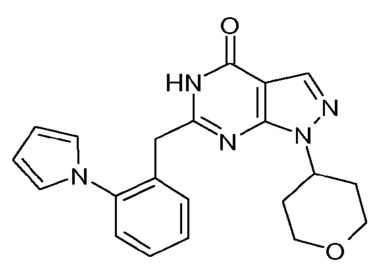
219	
220	
221	
222	
223	
224	
225	

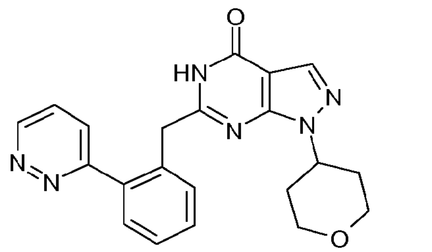
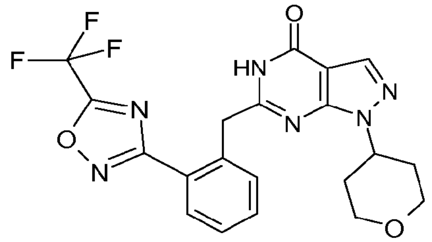
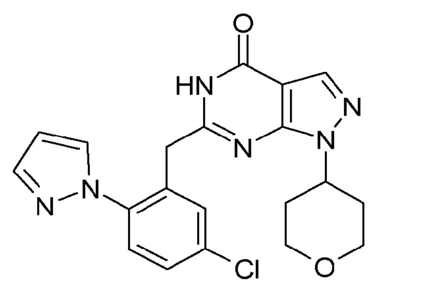
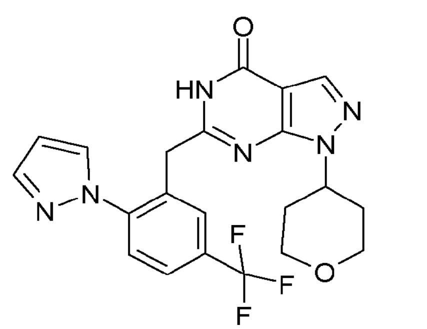
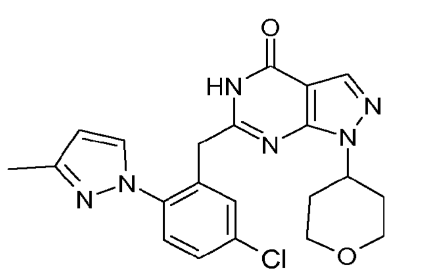
226	
227	
228	
229	
230	

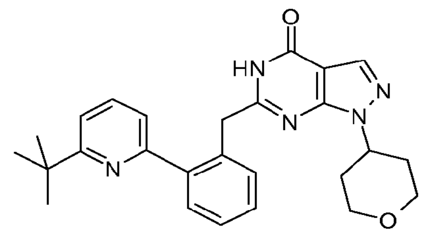
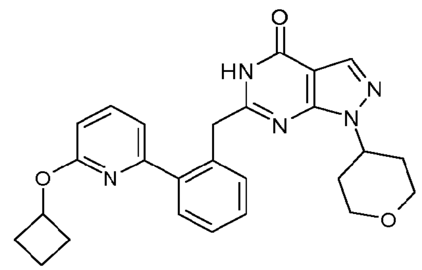
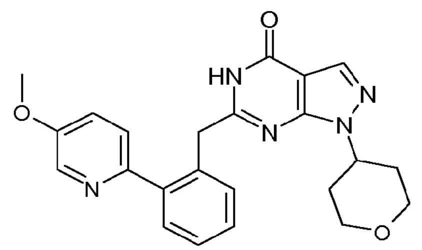
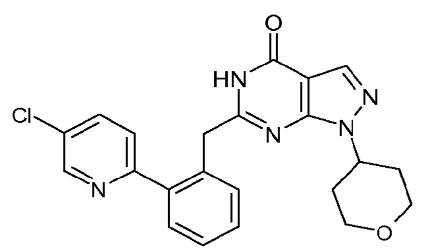
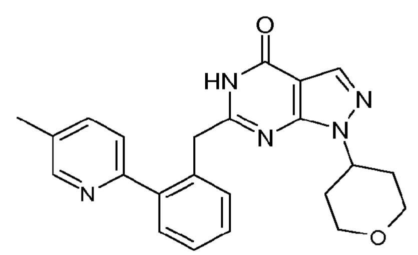
230-1	
230-2	
230-3	
230-5	

231	
232	
234	
239	
240	

241	
242	
243	
244	
245	

246	
247	
248	
249	
250	
251	
252	
253	

254	
255	
256	
257	
258	

259	
260	
261	
262	
263	

The invention also concerns the compounds of table 2, in form of the isoforms, tautomers, solvates, hydrates, or the salts of any of the listed compounds, particularly the physiologically acceptable salts thereof with inorganic or organic acids or bases, or the combinations thereof.

The above table (Table 2) also further illustrates general formula (I) and how to read the generic (genius) embodiments E-1 to E-24 of Table 1 and E-25 to E-48 of Table 3: for example compound 261, 6-[2-(5-Methoxy-pyridin-2-yl)-benzyl]-1-(tetrahydro-pyran-4-yl)-1,5-dihydro-pyrazolo[3,4-d]pyrimidin-4-one, corresponds with general formula (I) in that ***Hc*** is tetrahydropyran-4-yl, **V** and **W**, which build $\mathbf{R^1}$ (i.e. V-W-*), are defined as: **W** = phenyl, whereby said phenyl is attached via its 1 position to the CR^2R^3 group of formula (I); **V** = 5-Methoxy-pyridin-2-yl, whereby **V** is attached at the 2 position of **W** (i.e. **W** has a 1, 2 substitution pattern / ortho substitution); and R^2 and R^3 being H.

Further embodiments of the invention

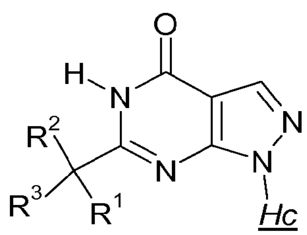
Another embodiment of the invention concerns compounds according to general formula (I), whereby the compounds are selected from the group of compounds of Table 2 with the example reference numbers: 219; 220; 221; 222; 223; 224; 225; 226; 227; 228; 229; 230; 230-1; 230-2; 230-3; 231; 232; 234; and where appropriate an isoform, tautomer, stereoisomer, solvate, hydrate, or a salts of any of these compounds, in particular a physiologically acceptable salts thereof with inorganic or organic acids or bases, or the combinations thereof.

Another embodiment according to the invention concerns ompounds according to general formula (I), whereby the compounds are selected from the group of compounds of Table 2 with the example reference numbers: 230-5; 239; 240; 241; 242; 243; 244; 245; 246; 247; 248; 249; 250; 251; 252; 253; 254; 255; 256; 257; 258; 259; 260; 261; 262; 263; and where appropriate an isoform, tautomer, stereoisomer, solvate, hydrate, or a salts of any of these compounds, in particular a physiologically

acceptable salts thereof with inorganic or organic acids or bases, or the combinations thereof.

Another set of embodiment of the invention is defined by Table 3.

Table 3: *a compound characterised by the general formula (I):*



(I),

with

	Hc	R^1	R^2	R^3
E-25	$\underline{Hc}^1$	$R^{1.1}$	defined by footnote[3)]	defined by footnote[4)]
E-26	$\underline{Hc}^1$	$R^{1.2}$	defined by footnote[3)]	defined by footnote[4)]
E-27	$\underline{Hc}^1$	$R^{1.3}$	defined by footnote[3)]	defined by footnote[4)]
E-28	$\underline{Hc}^1$	$R^{1.4}$	defined by footnote[3)]	defined by footnote[4)]
E-29	$\underline{Hc}^1$	$R^{1.5}$	defined by footnote[3)]	defined by footnote[4)]
E-30	$\underline{Hc}^1$	$R^{1.6}$	defined by footnote[3)]	defined by footnote[4)]
E-31	$\underline{Hc}^1$	$R^{1.5}$	being H	being H
E-32	$\underline{Hc}^1$	$R^{1.6}$	being H	being H
E-33	$\underline{Hc}^2$	$R^{1.1}$	defined by footnote[3)]	defined by footnote[4)]
E-34	$\underline{Hc}^2$	$R^{1.2}$	defined by footnote[3)]	defined by footnote[4)]

E-35	<u>Hc</u>^{2}	$R^{1.3}$	defined by footnote[3)]	defined by footnote[4)]
E-36	<u>Hc</u>^{2}	$R^{1.4}$	defined by footnote[3)]	defined by footnote[4)]
E-37	<u>Hc</u>^{2}	$R^{1.5}$	defined by footnote[3)]	defined by footnote[4)]
E-38	<u>Hc</u>^{2}	$R^{1.6}$	defined by footnote[3)]	defined by footnote[4)]
E-39	<u>Hc</u>^{2}	$R^{1.5}$	being H	being H
E-40	<u>Hc</u>^{2}	$R^{1.6}$	being H	being H

E-41	<u>Hc</u>^{3}	$R^{1.1}$	defined by footnote[3)]	defined by footnote[4)]
E-42	<u>Hc</u>^{3}	$R^{1.2}$	defined by footnote[3)]	defined by footnote[4)]
E-43	<u>Hc</u>^{3}	$R^{1.3}$	defined by footnote[3)]	defined by footnote[4)]
E-44	<u>Hc</u>^{3}	$R^{1.4}$	defined by footnote[3)]	defined by footnote[4)]
E-45	<u>Hc</u>^{3}	$R^{1.5}$	defined by footnote[3)]	defined by footnote[4)]
E-46	<u>Hc</u>^{3}	$R^{1.6}$	defined by footnote[3)]	defined by footnote[4)]
E-47	<u>Hc</u>^{3}	$R^{1.5}$	being H	being H
E-48	<u>Hc</u>^{3}	$R^{1.6}$	being H	being H

provided that the compound is not a compound selected from the group of compounds of Table 2 with the example reference numbers: 219; 220; 221; 222; 223; 224; 225; 226; 227; 228; 229; 230; 230-1; 230-2; 230-3; 231; 232; 234
or where appropriate an isoform, tautomer, stereoisomer, solvate, hydrate, or a salts of any of these compounds, in particular not a physiologically acceptable salts thereof with inorganic or organic acids or bases, or the combinations thereof.

Footnotes:

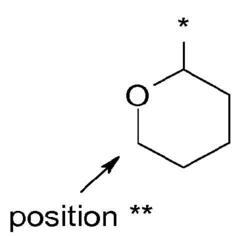
3) the definition refers to: **R^2** being selected from the group of H-, fluorine, F_3C-, HF_2C-, FH_2C-, and C_{1-3}-alkyl-, preferably **R^2** being H.

4) the definition refers to: **R^3** being selected from the group of H-, fluorine, F_3C-, HF_2C-, FH_2C-, and C_{1-3}-alkyl-, preferably **R^3** being H.

In all these embodiments of table 3 it is preferred that each of **R^2** and **R^3** is H.

Where appropriate, the subject matter of the invention also refers to the isoform, tautomer, stereoisomer, solvate, hydrate, or a salts of any of these compounds, in particular a physiologically acceptable salts thereof with inorganic or organic acids or bases, or the combinations thereof;

In another one embodiment of the invention it may be preferred that if ***Hc*** in any of the above described embodiments may be a group defined by the following formula D1



(D1),

whereby the * is the attachment point to the pyrazolo-group in general formula (I), then at the position ** there is no substituent that has an integral $-CH_2-$ group by which it is bound or even more preferably, at this positon ** there is no substituent at all.

In another embodiment of the invention it may be preferred in any of the aforementioned embodiments that for ***Hc*** being tetrahydropyranyl, then there is no CH_3-group that is bound at the alpha position to the ring oxygen atom.

In another embodiment of the invention it also may be preferred in any of the aforementioned embodiments that for ***<u>Hc</u>*** being tetrahydropyranyl, then there is no C_{1-6}-alkyl-group that is bound at the alpha position to the ring oxygen atom.

USED TERMS AND DEFINITIONS

Terms not specifically defined herein should be given the meanings that would be given to them by a person skilled in the art in light of the disclosure and the context. Examples include that specific substituents or atoms are presented with their 1 or 2 letter code, like H for hydrogen, N for nitrogen, C for carbon, O for oxygen, S for sulphur and the like. Optionally but not mandatory the letter is followed by a hyphen to indicate a bond. As used in the specification, unless specified to the contrary, the following terms have the meaning indicated and the following conventions are adhered to.

In the groups, radicals, or moieties defined below, the number of carbon atoms is often specified preceding the group, for example, C_{1-6}-alkyl means an alkyl group or alkyl radical having 1 to 6 carbon atoms. In general, for groups that are composed of two or more subgroups, the last named group is the radical attachment point, for example, "alkyl-O-" means a monovalent radical of the formula alkyl-O-, which is attached via the oyxygen atom thereof (i.e. alkoxy). If the term of a substituent starts or ends with a minus sign or hyphen, i.e. - this sign emphasises the attachment point like in the aforementioned example alkyl-O-, where the “O” is linked to the group of which the alkyl-O- is a substituent. Unless otherwise specified below, conventional definitions of terms control and conventional stable atom valences are presumed and achieved in all formulas and groups.

In general, if terms are specifically defined with a given context, such specific definitions shall prevail the more general definitions as outlined in this paragraph.

In general, all “**tautomeric forms and isomeric forms and mixtures**”, whether individual geometric isomers or optical isomers or racemic or non-racemic mixtures of isomers, of a chemical structure or compound are intended, unless the specific

stereochemistry or isomeric form is specifically indicated in the compound name or structure. Specific definitions prevail.

The term "**substituted**" as used herein explicitly or implicitly, means that any one or more hydrogen(s) on the designated atom is replaced with a member of the indicated group of substituents, provided that the designated atom's normal valence is not exceeded. In case a substituent is bound via a double bond, e.g. an oxo substituent, such substituent replaces two hydrogen atoms on the designated atom. The substitution shall result in a stable compound. “Stable” in this context preferably means a compound that from a pharmaceutical point of view is chemically and physically sufficiently stable in order to be used as an active pharmaceutical ingredient of a pharmaceutical composition.
If a substituent is not defined, it shall be hydrogen.

By the term "**optionally substituted**" is meant that either the corresponding group is substituted or it is not.

The phrase "**pharmaceutically acceptable**" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

As used herein, "**pharmaceutically acceptable salt(s)**" refer to derivatives of the disclosed compounds wherein the parent compound is modified by making acid or base salts thereof preferably addition salts. Examples of pharmaceutically acceptable salts of a compound according to the invention that has a basic function (e.g. an aminogroup) include, but are not limited to, mineral or organic acid salts; and the like. Compounds with acidic properties may form salts with alkali or organic bases. The pharmaceutically acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric acid, hydrobromic

acid, sulfuric acid, sulfamic acid, phosphoric acid, nitric acid, and the like; and the salts prepared from organic acids such as acetic acid, propionic acid, succinic acid, glycolic acid, stearic acid, lactic acid, malic acid, tartaric acid, citric acid, ascorbic acid, pamoic acid, maleic acid, hydroxymaleic acid, phenylacetic acid, glutamic acid, benzoic acid, salicylic acid, sulfanilic acid, 2-acetoxybenzoic acid, fumaric acid, toluenesulfonic acid, methanesulfonic acid, ethane disulfonic acid, oxalic acid, isethionic acid, and the like.

The pharmaceutically acceptable salts of the present invention can be synthesized from the parent compound with basic or acidic properties by conventional chemical methods. Generally, such salts can be prepared by reacting a compound of the present invention that has basic properties with a stoichiometric amount of the appropriate acid (respectively, compounds with acidic properties with a stoichiometric amount of the appropriate base) in water or in an organic solvent, or in a mixture of the two; generally, non-aqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred.

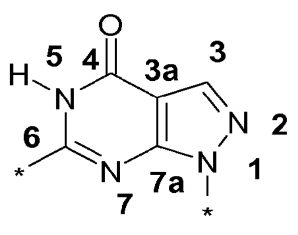
"**Prodrugs**" are considered compounds that release an active parent drug of the present invention in vivo when such prodrug is administered to a mammalian subject. Prodrugs according to the present invention are prepared by modifying functional groups present in the compound of the invention in such a way that these modifications are retransformed to the original functional groups under physiological conditions. Prodrugs include compounds of the present invention wherein a hydroxy, amino, or sulfhydryl group is bound to any group that, when the prodrug of the present invention is administered to a mammalian subject, is retransformed to free said hydroxyl, amino, or sulfhydryl group. Examples of prodrugs include, but are not limited to, acetate, formate and benzoate derivatives of alcohol and amine functional groups in the compounds of the present invention.

"**Metabolites**" are considered as derivatives of the compounds according to the present invention that are formed in vivo. Active metabolites are such metabolites that cause a pharmacological effect. It will be appreciated that metabolites of the

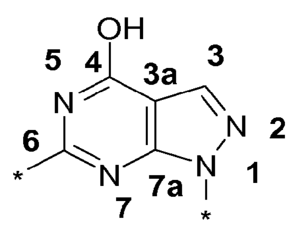
compounds according to the present inventions are subject to the present invention as well, in particular active metabolites.

Some of the compounds may form "**solvates**". For the purposes of the invention the term "solvates" refers to those forms of the compounds which form, in the solid or liquid state, a complex by coordination with solvent molecules. Hydrates are a specific form of solvates in which the coordination takes place with water. According to the present invention, the term preferably is used for solid solvates, such as amorphous or more preferably crystalline solvates.

"**Scaffold**": The scaffold of the compounds according to the present invention is represented by the following core structure. The numeration of the positions of the ring member atoms is indicated in bold:



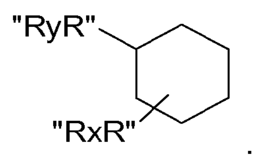
It will be evident for the skilled person in the art, that this scaffold can be described by its tautomeric "enol" form



In the context of the present invention both structural representations of the scaffold shall be considered the subject of the present invention, even if only one of the two

representatives is presented. Without meant to be limiting or being bound, it is believed that for the majority of compounds under ambient conditions and therewith under conditions which are the relevant conditions for a pharmaceutical composition comprising said compounds, the equilibrium of the tautomeric forms lies on the side of the pyrazolopyrimdin-4-one representation. Therefore, all embodiments are presented as pyrazolopyrimdin-4-one-derivatives or more precisely as pyrazolo[3,4-d]pyrimidin-4-one derivatives.

"**Bonds**": If within a chemical formula of a ring system or a defined group a substituent is directly linked to an atom or a group like "RyR" in below formula this shall mean that the substituent is only attached to the corresponding atom. If however from a substituent like "RxR" a bond is not specifically linked to an atom of the ring system but drawn towards the centre of the ring or group this means that this substituent "RxR" may be linked to any meaningful atom of the ring system / group unless stated otherwise.



The bond symbol "-" (= minus sign) or the symbol "- *" (= minus sign followed by an asterisk sign) stands for the bond through which a substituent is bound to the corresponding remaining part of the molecule / scaffold. In cases in that the minus sign does not seem to be sufficiently clear, there may be added an asterisk to the bond symbol "-" in order to determine the point of attachment of said bond with the corresponding main part of the molecule / scaffold.

In general, the bond to one of the herein defined heterocycloalkyl or heteroaryl groups may be effected via a carbon ring atom or optionally via a nitrogen ring atom of such heterocycloalkyl or heteroaryl group.

The term "**aryl**" used in this application denotes a phenyl, biphenyl, indanyl, indenyl, 1,2,3,4-tetrahydronaphthyl or naphthyl group, preferably it denotes a phenyl or naphtyl group, more preferably a phenyl group. This definition applies for the use of "**aryl**" in any context within the present description in the absence of a further definition.

The term "**C_{1-n}-alkyl**" denotes a saturated, branched or unbranched hydrocarbon group with 1 to n C atoms, wherein n is a figure selected from the group of 2, 3, 4, 5 or 6. Examples of such groups include methyl, ethyl, *n*-propyl, *iso*-propyl, butyl, *iso*-butyl, *sec*-butyl, *tert*-butyl, *n*-pentyl, *iso*-pentyl, *neo*-pentyl, *tert*-pentyl, *n*-hexyl, *iso*-hexyl etc.
This definition applies for the use of "**alkyl**" in any reasonable context within the present description in the absence of a further definition.
In cases in which the term "**C_{1-n}-alkyl**" is used in the middle of two other groups / substituents, like for example in **"C_{1-n}-cycloalkyl-C_{1-n}-alkyl-O-",** this means that the "C_{1-n}-alkyl"-moiety bridges said two other groups. In the present example it bridges the C_{1-n}-cycloalkyl with the oxygen like in "cyclopropyl-methyl-oxy-". It will be evident, that in such cases "C_{1-n}-alkyl" has the meaning of a "C_{1-n}-alkylene" spacer like methylene (-CH_2 -), ethylene (e.g. -CH_2 - CH_2 -), etc. The groups that are bridged by "C_{1-n}-alkyl" may be bound to "C_{1-n}-alkyl" at any position thereof. Preferably the right hand group is located at the distal right hand end of the alkyl group and left hand group at the distal left hand side of the alkyl group (e.g. for HO-C_3-alkyl-: 3-hydroxy-propan-1-yl). The same applies for other substituents.

The term "**C_{3-n}-cycloalkyl**" denotes a saturated monocyclic group with 3 to n C ring atoms. n preferably has a value of 4 to 7 (= 4, 5, 6 or 7). There are no ring atoms other than carbon atoms. Examples of such groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl etc.. This definition applies for "**cycloalkyl**" in any reasonable context within the present description in the absence of a further definition.

The term “**heteroaryl**” used in this application denotes a heterocyclic, mono- or bicyclic aromatic ring system which includes within the ring system itself in addition to at least one C atom one or more heteroatom(s) independently selected from N, O, and/or S. A monocyclic ring system preferably consists of 5 to 6 ring members, a bicyclic ring system preferably consists of 8 to 10 ring members. Preferred are heteroaryls with up to 3 heteroatoms, more preferred up to 2 heteroatoms, more preferred with 1 heteroatom. Preferred heteroatom is N. Examples of such moieties are benzimidazolyl, benzisoxazolyl, benzo[1,4]-oxazinyl, benzoxazol-2-onyl, benzofuranyl, benzoisothiazolyl, 1,3-benzodioxolyl, benzothiadiazolyl, benzothiazolyl, benzothienyl, benzoxadiazolyl, benzoxazolyl, chromanyl, chromenyl, chromonyl, cinnolinyl, 2,3-dihydrobenzo[1,4]dioxinyl, 2,3-dihydrobenzofuranyl, 3,4-dihydrobenzo[1,4]oxazinyl, 2,3-dihydroindolyl, 1,3-dihydroisobenzofuranyl, 2,3-dihydroisoindolyl, 6,7-dihydropyrrolizinyl, dihydroquinolin-2-onyl, dihydroquinolin-4-onyl, furanyl, imidazo[1,2-*a*]pyrazinyl, imidazo[1,2-*a*]pyridyl, imidazolyl, imidazopyridyl, imidazo[4,5-d]thiazolyl, indazolyl, indolizinyl, indolyl, isobenzofuranyl, isobenzothienyl, isochromanyl, isochromenyl, isoindoyl, isoquinolin-2-onyl, isoquinolinyl, isothiazolyl, isoxazolyl, naphthyridinyl, 1,2,4-oxadiazoyl, 1,3,4-oxadiazoyl, 1,2,5-oxadiazoyl, oxazolopyridyl, oxazolyl, 2-oxo-2,3-dihydrobenzimidazolyl, 2-oxo-2,3-dihydroindolyl, 1-oxoindanyl, phthalazinyl, pteridinyl, purinyl, pyrazinyl, pyrazolo[1,5-*a*]pyridyl, pyrazolo[1,5-*a*]pyrimidinyl, pyrazolyl, pyridazinyl, pyridopyrimidinyl, pyridyl (pyridinyl), pyridyl-*N*-oxide, pyrimidinyl, pyrimidopyrimidinyl, pyrrolopyridyl, pyrrolopyrimidinyl, pyrrolyl, quinazolinyl, quinolin-4-onyl, quinolinyl, quinoxalinyl, 1,2,3,4-tetrahydroquinolinyl, 1,2,3,4-tetrahydroisoquinolinyl, tetrazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, thiazolyl, thieno[2,3-*d*]imidazolyl, thieno[3,2-*b*]pyrrolyl, thieno[3,2-*b*]thiophenyl, thienyl, triazinyl, or triazolyl.

Preferred heteroaryl groups are defined in the corresponding context.

The definition pyrazole includes the isomers 1H-, 3H- and 4H-pyrazole. Preferably pyrazolyl denotes 1H-pyrazolyl.

The definition imidazole includes the isomers 1H-, 2H- and 4H-imidazole. A preferred definition of imidazolyl is 1H-imidazolyl.

The definition triazole includes the isomers 1H-, 3H- and 4H-[1,2,4]-triazole as well as 1H-, 2H- and 4H-[1,2,3]-triazole. The definition triazolyl therefore includes 1H-[1,2,4]-triazol-1-, -3- and -5-yl, 3H-[1,2,4]-triazol-3- and -5-yl, 4H-[1,2,4]-triazol-3-, -4- and -5-yl, 1H-[1,2,3]-triazol-1-, -4- and -5-yl, 2H-[1,2,3]-triazol-2-, -4- and -5-yl as well as 4H-[1,2,3]-triazol-4- and -5-yl.

The term tetrazole includes the isomers 1H-, 2H- and 5H-tetrazole. The definition tetrazolyl therefore includes 1H-tetrazol-1- and -5-yl, 2H-tetrazol-2- and -5-yl and 5H-tetrazol-5-yl.

The definition indole includes the isomers 1H- and 3H-indole. The term indolyl preferably denotes 1H-indol-1-yl.

The term isoindole includes the isomers 1H- and 2H-isoindole.

This definition applies for "**heteroaryl**" in any reasonable context within the present description in the absence of a further definition.

The term **"heterocycloalkyl**" within the context of the present invention denotes a saturated 3 to 8 membered, preferably 5-, 6- or 7-membered ring system or a 5-12 membered bicyclic ring system, the ring atoms of which are carbon atoms and 1, 2, 3 or 4 heteroatoms, selected from N, O, and/or S, the S optionally in form of SO or SO_2. Preferred are 1, 2, or 3, more preferred 1 heteroatoms.
The preferred number of carbon ring atoms is 3 to 7 beside said 1, 2, 3 or 4 heteroatoms selected from N, O, and/or S. Such heterocycloalkyl groups are addressed as C_{3-7}-heterocycloalkyl.
Preferred are saturated heterocycloalkyl rings with 5, 6, or 7 ring atoms, of which 1 or 2 are heteroatoms and the remaining are C-atoms.

Preferred example for heterocycloalkyl include morpholinyl, piperidinyl, piperazinyl, thiomorpholinyl, oxathianyl, dithianyl, dioxanyl, pyrrolidinyl, tetrahydrofuranyl, dioxolanyl, oxathiolanyl, imidazolidinyl, tetrahydropyranyl, pyrrolinyl, tetrahydrothienyl, oxazolidinyl, homopiperazinyl, homopiperidinyl, homomorpholinyl, homothiomorpholinyl, azetidinyl, 1,3-diazacyclohexanyl or pyrazolidinyl group.

This definition applies for “**heterocycloalkyl**” in any reasonable context within the present description in the absence of a further specific definition.

The term “**oxo**” denotes an oxygen atom as substituent that is bonded by a double bond, preferably it is bonded to a C-atom. In case oxo is used as a substituent, the oxo replaces two hydrogen atoms of the corresponding atom of the unsubstituted compound.

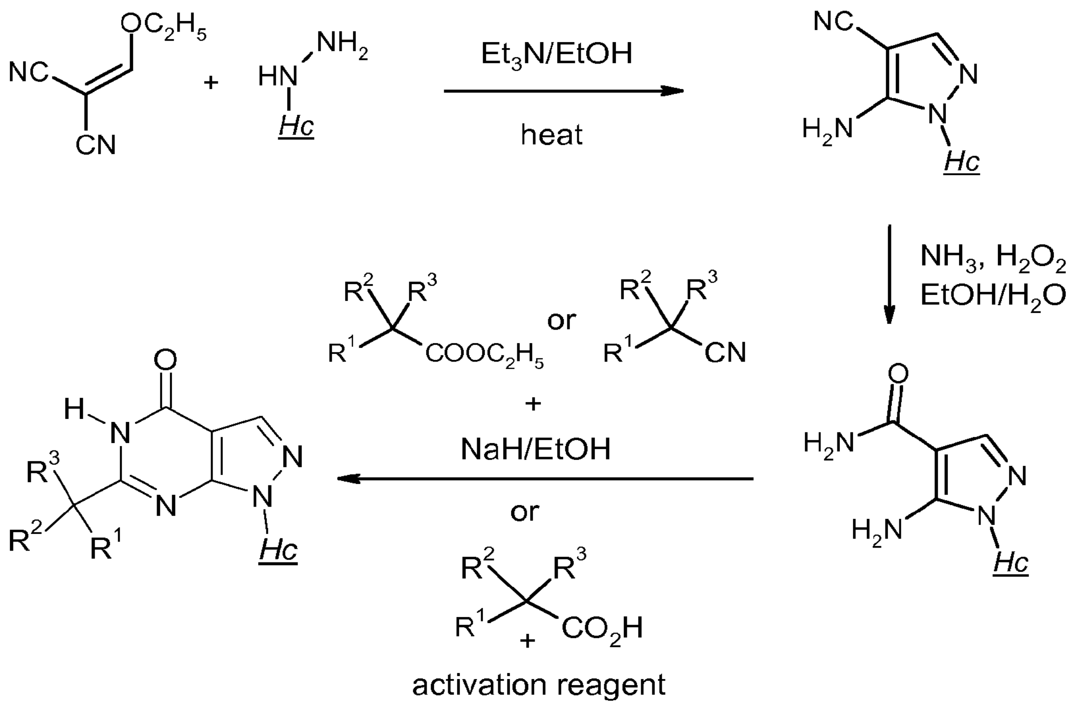
The terms “**pyridyl**” and “**pyridinyl**” are used equally (in parallel) to define a pyridine-substituent.

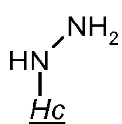
The expressions "**prevention**", "**prophylaxis**", "**prophylactic treatment**" or "**preventive treatment**" used herein should be understood synonymous and in the sense that the risk to develop a condition mentioned hereinbefore is reduced, especially in a patient having elevated risk for said conditions or a corresponding anamnesis. Thus the expression "prevention of a disease" as used herein means the management and care of an individual at risk of developing the disease prior to the clinical onset of the disease. The purpose of prevention is to combat the development of the disease, condition or disorder, and includes the administration of the active compounds to prevent or delay the onset of the symptoms or complications and to prevent or delay the development of related diseases, conditions or disorders. Success of said preventive treatment is reflected statistically by reduced incidence of said condition within a patient population at risk for this condition in comparison to an equivalent patient population without preventive treatment.

The expression "**treatment**" or "**therapy**" preferably means therapeutic treatment of (e.g.human) patients having already developed one or more of said conditions in manifest, acute or chronic form, including symptomatic treatment in order to relieve symptoms of the specific indication or causal treatment in order to reverse or partially reverse the condition or to delay the progression of the indication as far as this may be possible, depending on the condition and the severity thereof. Thus the expression "treatment of a disease" as used herein means the management and care of a patient having developed the disease, condition or disorder. The purpose of treatment is to combat the disease, condition, disorder or a symptom thereof. Treatment includes the administration of the active compounds to eliminate or control the disease, condition or disorder as well as to alleviate the symptoms or complications associated with the disease, condition or disorder.

The following schemes shall illustrate generally ways to manufacture the compounds of the present invention by way of example. The abbreviated substituents may be as defined for the embodiments of formula (I) if not defined otherwise within the context fo the schemes:

Scheme 1



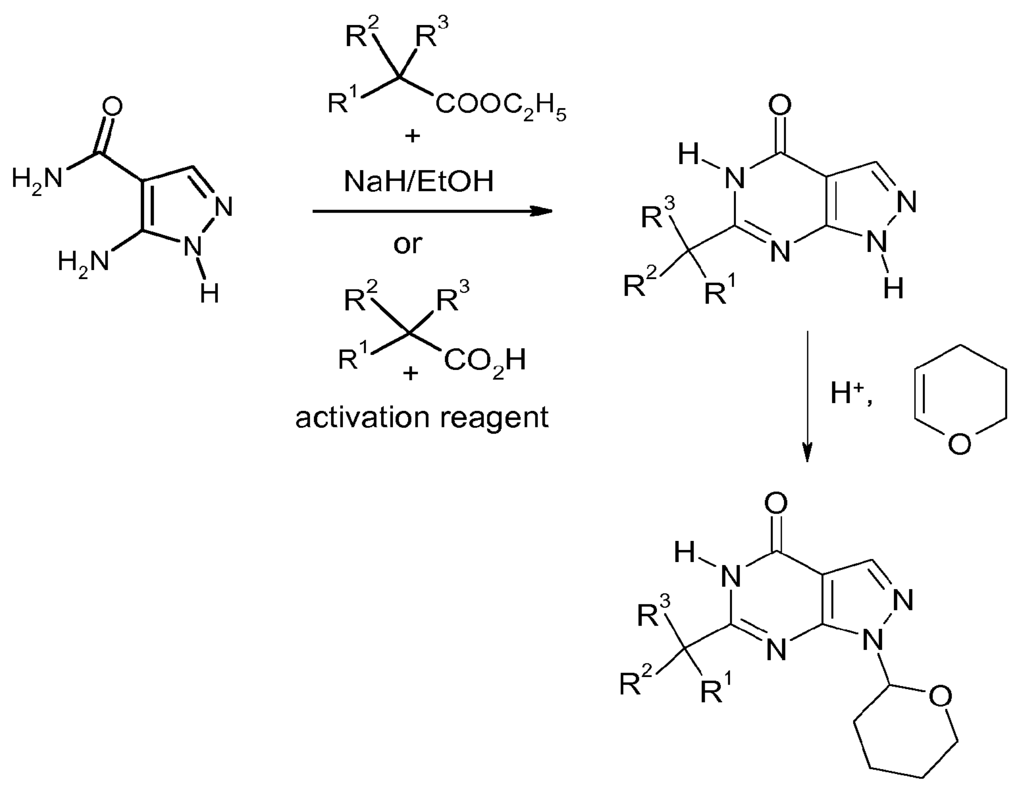


: the hyrazino-group is bound to a C-atom of the tetrahydropyranyl-group.

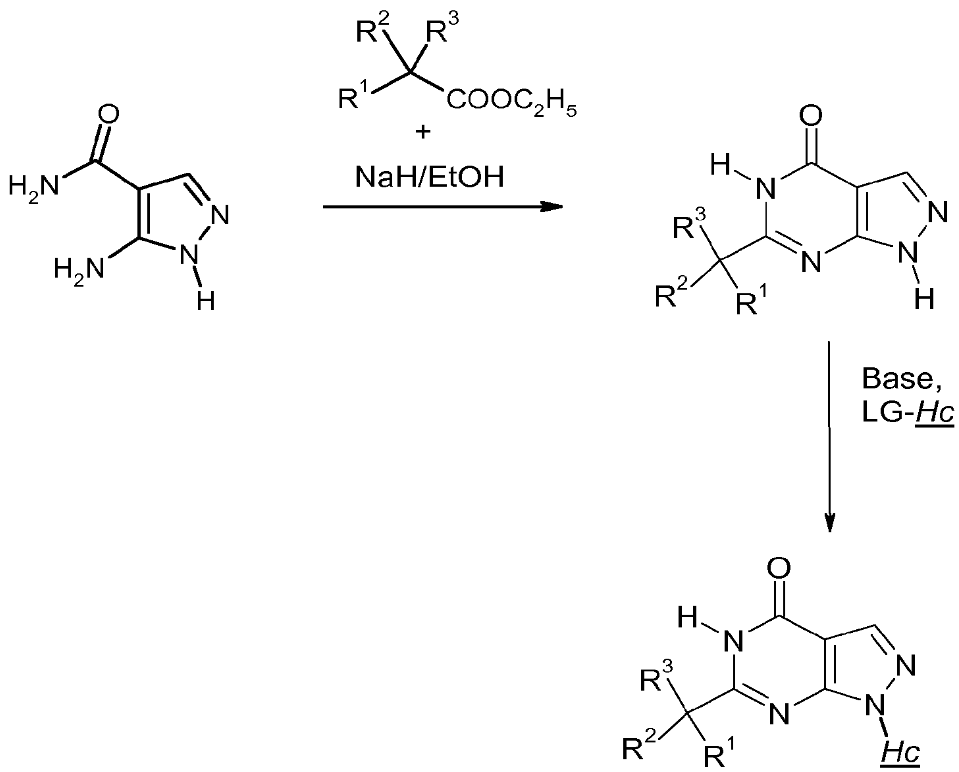
Scheme 1: In a first step 2-ethoxymethylene-malononitrile is condensed with mono-substituted hydrazines by heating in an appropriate solvent like ethanol in the presence of a base (e.g. triethylamine) to form the corresponding 5-amino-1H-pyrazole-4-carbonitriles. These compounds are converted in a second step to the corresponding amides, e.g. by treatment of an ethanolic solution with ammonia (25 % in water) and hydrogen peroxide (35 % in water). In a third step, heating with carboxylic esters under basic conditions (e.g sodium hydride in ethanol) or carboxylic acids with an activation reagent (e.g. polyphosporic acid) leads to pyrazolo[3,4-d]pyrimidin-4-ones as final products [cf., for example, A. Miyashita *et al.*, *Heterocycles* **1990**, *31*, 1309ff].

Schemes 2 and 3 illustrate alternative methods to prepare the final compounds: in these exemplified manufacturing methods 5-amino-1H-pyrazole-4-carboxylic acid amides are condensed in a first step with an appropriate ester derivative followed in a second step by alkylation with suitable electrophiles.

Scheme 2



Scheme 3

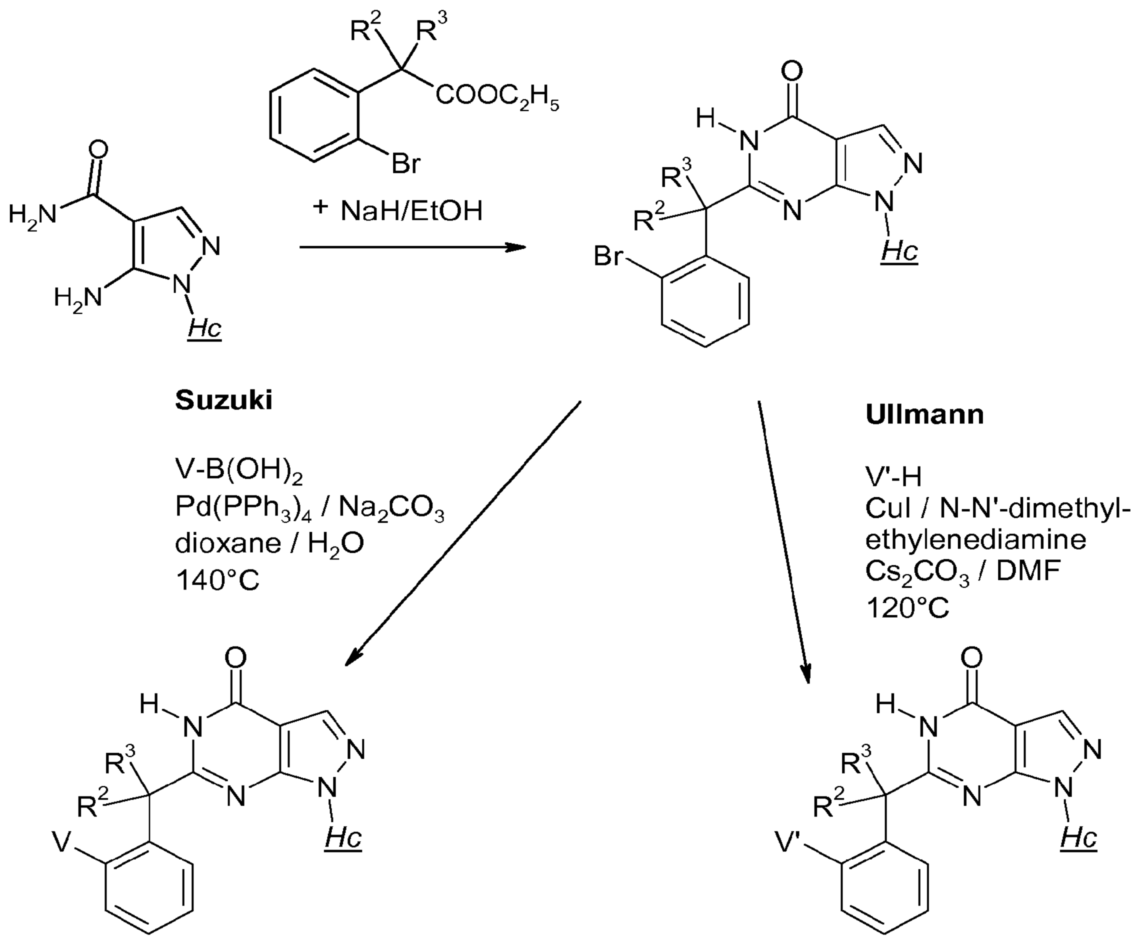


LG = Br-, Cl-, I-, CH_3-SO_2-O-, p-toluenesulphonyl-, which is bound to *Hc* by one of the ring carbon atoms of the tetrahydropyranoyl group.

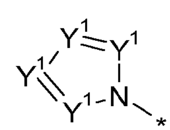
Base = $N(C_2H_5)_3$, KO*t*Bu, NaH

Schemes 4 and 5 illustrate alternative methods to prepare the final compounds: in the exemplified manufacturing methods 5-amino-1H-pyrazole-4-carboxylic acid amides are condensed in a first step with (2-bromo-phenyl)-acetic acid ester derivatives followed in a second step by substitution of the bromine atom by an aromatic or heteroaromatic residue e.g. using Suzuki or Ullmann type reaction conditions. Alternatively, as depicted in scheme 5, the aromatic or heteroaromatic residue is first inserted into a phenyl-acetonitrile residue and condensed with 5-amino-1H-pyrazole-4-carboxylic acid amides in a second step.

Scheme 4

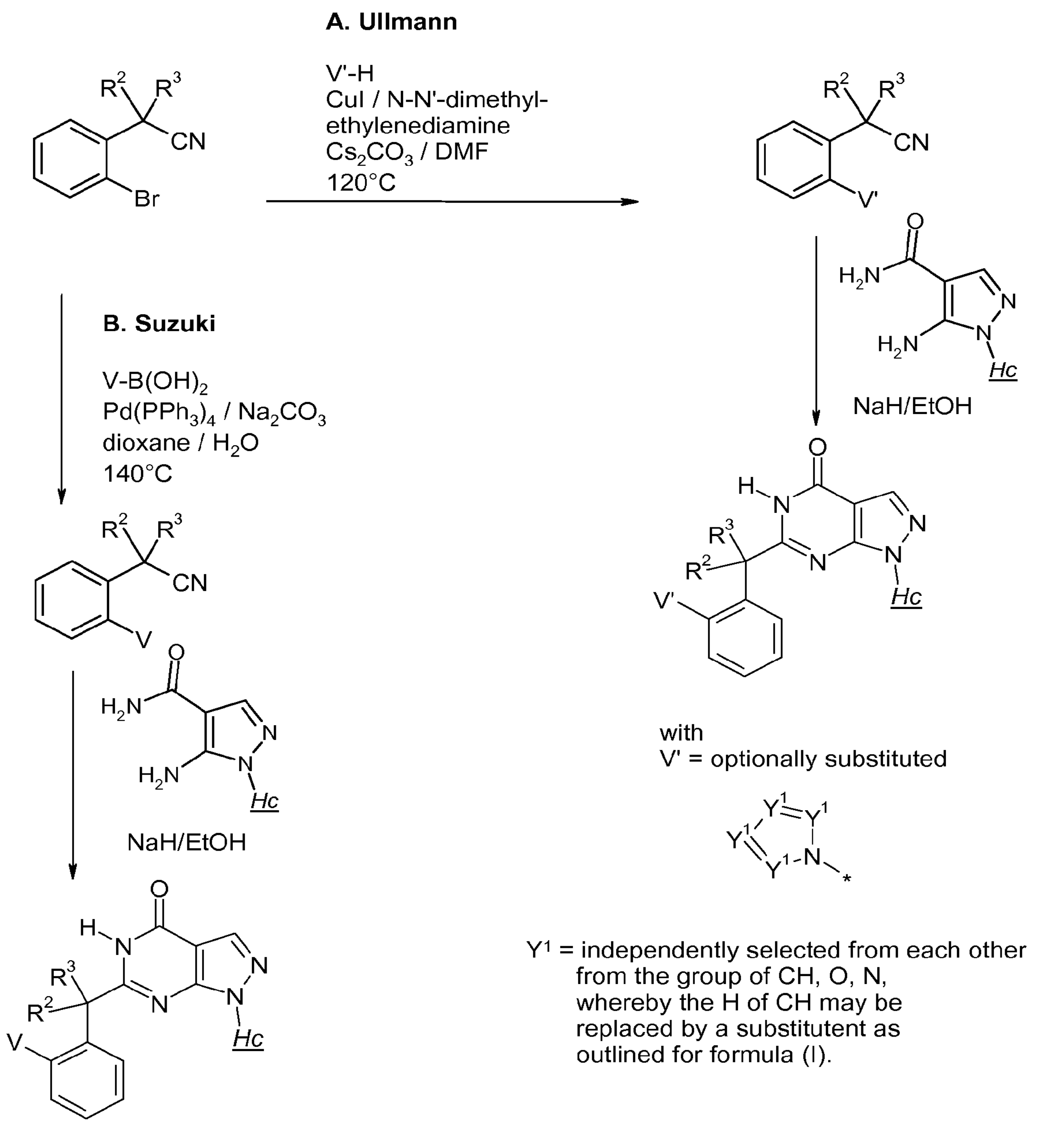


with
V' = optionally substituted



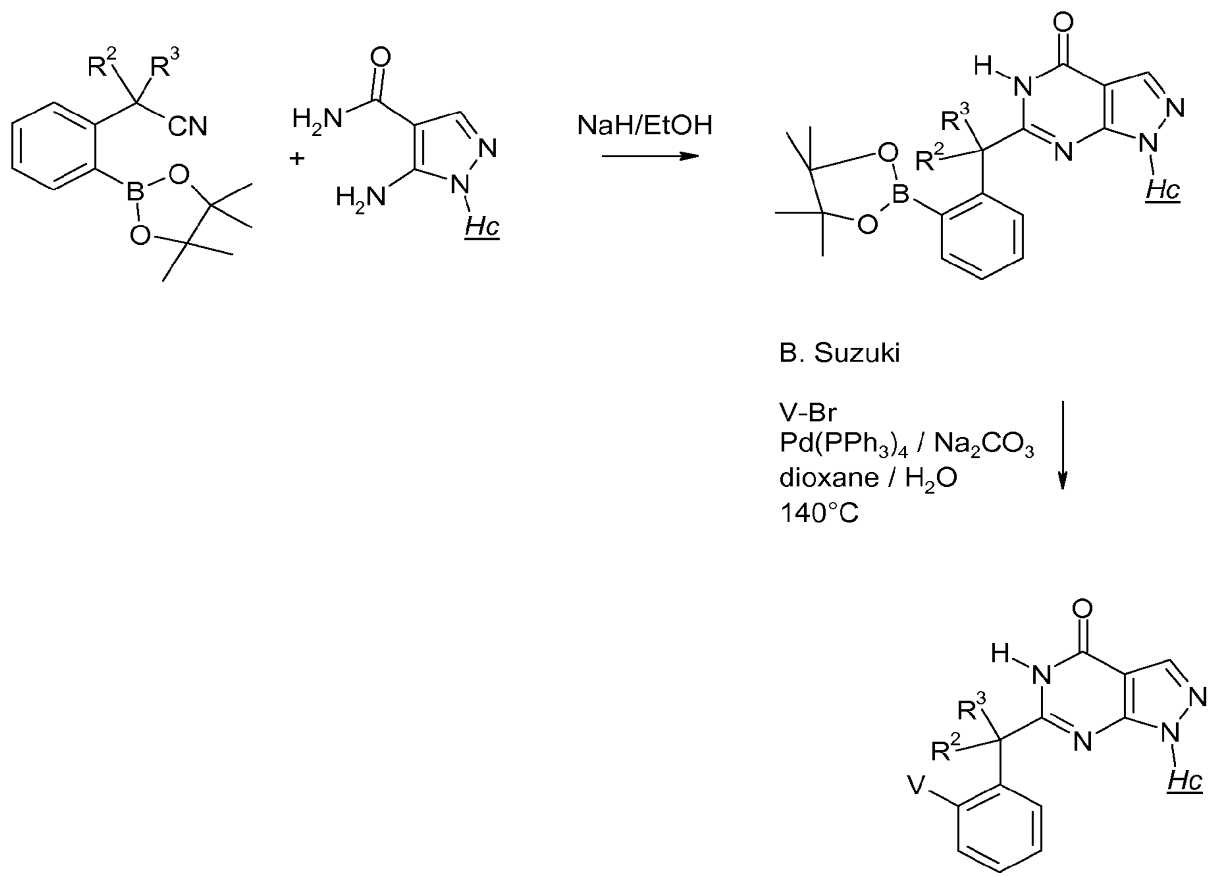
Y^1 = independently selected from each other from the group of CH, O, N, whereby the H of CH may be replaced by a substitutent as outlined for formula (I).

Scheme 5



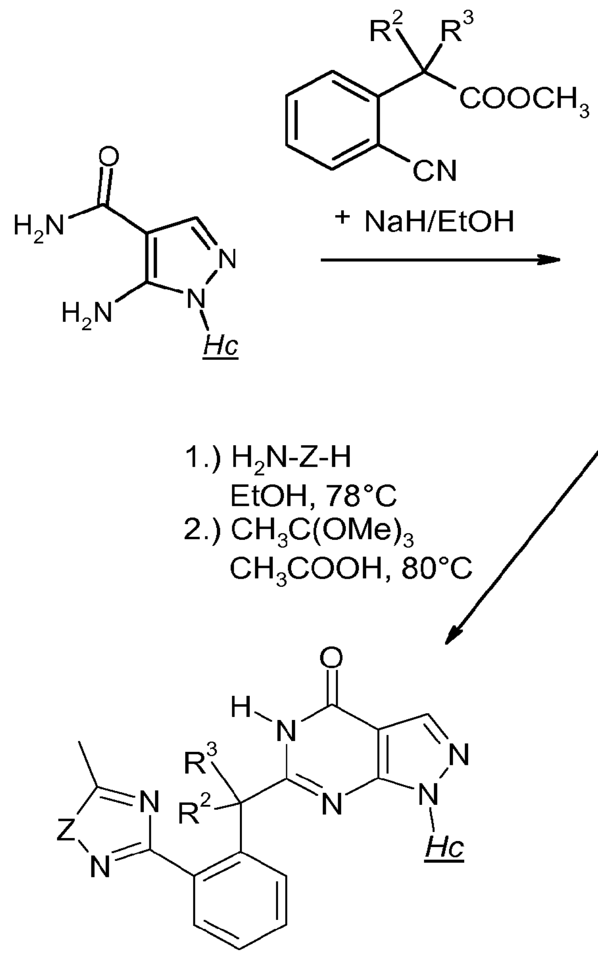
Furthermore, the synthesis of final compounds can also be accomplished through the preparation of a boronic acid derivative, followed by a Suzuki type cross coupling in a second step (Scheme 6).

Scheme 6



Scheme 7 illustrates an alternative method to prepare the final compounds: in the exemplified manufacturing method 5-amino-1H-pyrazole-4-carboxylic acid amides are condensed in a first step with (2-cyano-phenyl)-acetic acid ester derivatives followed in a second step by transformation of the nitrile group into a 5-membered heteroaromatic group.

Scheme 7



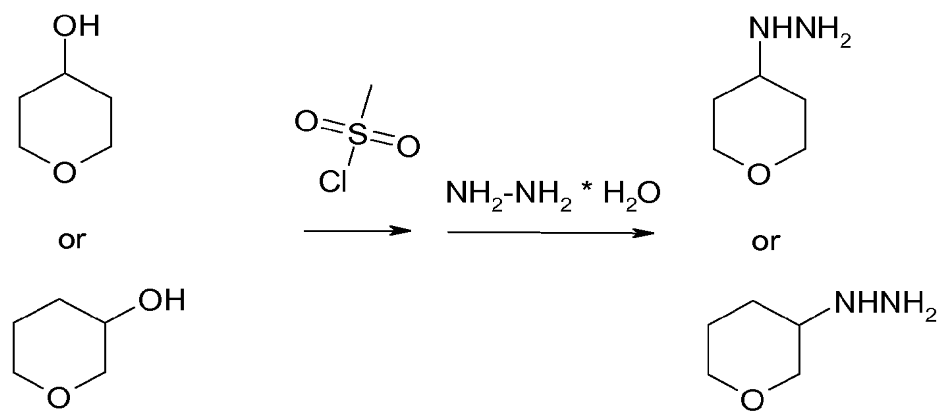
with
Z = O or NH

Further alternative processes for preparing pyrazolo[3,4-d]pyrimidin-4-ones are known in the art and can likewise be employed for synthesizing the compounds of the invention (see, for example: P. Schmidt *et al.*, *Helvetica Chimica Acta* **1962**, *189*, 1620ff.).

The mono-substituted hydrazine derivatives, that are used in step 1 of scheme 1 can be prepared either by nucleophilic displacement on the corresponding mesylate derivative (scheme 8) or by reduction of the hydrazone intermediate as depicted in scheme 9 [cf.,

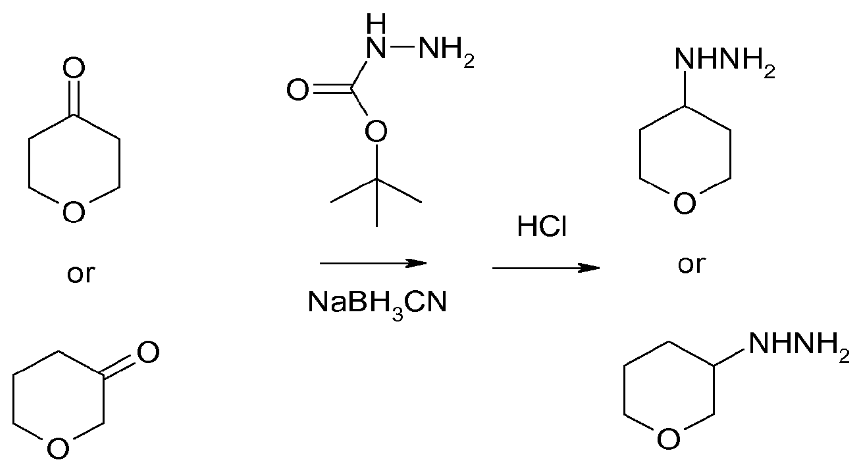
for example, J.W. Timberlake *et al.*, "*Chemistry of Hydrazo-,Azo-, and Azoxy Groups"; Patai,S.,Ed.;* 1975, *Chapter 4*; S. C. Hung *et al.*, *Journal of organic Chemistry 1981*, 46, 5413-5414].

Scheme 8



The tetrahydropyranyl-group optionally may be further substituted as defined.

Scheme 9



The tetrahydropyranyl-group optionally may be further substituted as defined.

Further information also can be found in WO04099210 (in particular page 9, last paragraph to page 14, line 8, incorporated by reference).

The compounds of the invention show a valuable range of pharmacological effects which could not have been predicted. They are characterised in particular by inhibition of PDE9A.

Preferably the compounds according to the present invention show a high selectivity profile in view of inhibiting or modulating specific members within the PDE9 family or other PDE families, with a clear preference (selectivity) towards PDE9A inhibition.

The compounds of the present invention are supposed to show a favourable safety profile for the purpose of medical treatment.

The compounds of the present invention are supposed to show a favourable profile with respect to metabolic stability over a certain period of time for the purpose of medical treatment.

The compounds of the present invention are supposed to show a favourable profile with respect to bioavailability for the purpose of medical treatment.

METHOD OF TREAMENT

The present invention refers to compounds, which are considered effective in the treatment of diseases. The compounds according to the invention are effective and selective inhibitors of phosphodiesterase 9A and can be used for the development of medicaments. Such medicaments shall preferably be used for the treatment of diseases in which the inhibition of PDE9A can evolve a therapeutic, prophylactic or disease modifying effect. Preferably the medicaments shall be used to improve perception, concentration, cognition, learning or memory, like those occurring in particular in situations/diseases/syndromes such as: mild cognitive impairment, age-associated learning and memory impairments, age-associated memory losses, vascular dementia, craniocerebral trauma, stroke, dementia occurring after strokes (post stroke dementia), post-traumatic dementia, general concentration impairments, concentration impairments in children with learning and memory problems, Alzheimer's disease, Lewy body dementia, dementia with degeneration of the frontal lobes, including Pick's syndrome, Parkinson's disease, progressive nuclear palsy,

dementia with corticobasal degeneration, amyotropic lateral sclerosis (ALS), Huntington's disease, multiple sclerosis, thalamic degeneration, Creutzfeld-Jacob dementia, HIV dementia, epilepsy, temporal lobe epilepsy, schizophrenia or Korsakoff's psychosis.

Another aspect of the present invention concerns the treatment of a disease which is accessible by PDE9A modulation, in particular sleep disorders like insomnia or narcolepsy, bipolar disorder, metabolic syndrome, obesity, diabetes mellitus, including type 1 or type 2 diabetes, hyperglycemia, dyslipidemia, impaired glucose tolerance, or a disease of the testes, brain, small intestine, skeletal muscle, heart, lung, thymus or spleen.

Thus, the medical aspect of the present invention can be summarised in that it is considered that a compound according to any of the generic (genius) embodiments of the invention as outlined herein or a compound selected from the group of the specifically disclosed ones (“species”) is used as a medicament.

Such a medicament preferably is for the treatment of a CNS disease.

In an alternative use, the medicament is for the treatment of a CNS disease, the treatment of which is accessible by the inhibition of PDE9.

In an alternative use, the medicament is for the treatment of a disease that is accessible by the inhibition of PDE9, specifically PDE9A.

In an alternative use, the medicament is for the treatment, amelioration and / or prevention of cognitive impairment being related to perception, concentration, cognition, learning or memory.

In an alternative use, the medicament is for the treatment, amelioration and / or prevention of cognitive impairment being related to age-associated learning and memory impairments, age-associated memory losses, vascular dementia, craniocerebral trauma, stroke, dementia occurring after strokes (post stroke dementia), post-traumatic dementia, general concentration impairments, concentration impairments in children with learning and memory problems,

Alzheimer's disease, Lewy body dementia, dementia with degeneration of the frontal lobes, including Pick's syndrome, Parkinson's disease, progressive nuclear palsy, dementia with corticobasal degeneration, amyotropic lateral sclerosis (ALS), Huntington's disease, multiple sclerosis, thalamic degeneration, Creutzfeld-Jacob dementia, HIV dementia, epilepsy, temporal lobe epilepsy, schizophrenia with dementia or Korsakoff's psychosis.

In an alternative use, the medicament is for use in the treatment of Alzheimer's disease.

In an alternative use, the medicament is for the treatment of sleep disorders, bipolar disorder, metabolic syndrome, obesity, diabetis mellitus, hyperglycemia, dyslipidemia, impaired glucose tolerance, or a disease of the testes, brain, small intestine, skeletal muscle, heart, lung, thymus or spleen.

In a further aspect of the invention, the present invention relates to the method of treatment or prevention of a condition or disease selected fromt the above listed groups of conditions and diseases, whereby the method comprises the administration of a therapeutically effective amount of a compound according to the invention in a human being in need thereof.

PHARMACEUTICAL COMPOSITIONS

Medicaments for administration, which are also subject to the present invention, comprise a compound according to the present invention in a therapeutically effective amount and a pharmaceutical carrier. By "therapeutically effective amount" it is meant that if the medicament is applied via the appropriate regimen adapted to the patient's condition, the amount of said compound of formula (I) will be sufficient to effectively treat, to prevent or to decelerate the progression of the corresponding disease, or otherwise to ameliorate the estate of a patient suffering from such a disease. It may be the case that the "therapeutically effective amount" in a mono-therapy will differ from the "therapeutically effective amount" in a combination therapy with another medicament.

The dose range of the compounds of general formula (I) applicable per day may be from 0.1 to 5000 mg, preferably from 0.1 to 1000 mg, preferably from 2 to 500 mg, more preferably from 5 to 250 mg, most preferably from 10 to 100 mg. A dosage unit (e.g. a tablet) preferably may contain between 2 and 250 mg, particularly preferably between 10 and 100 mg of the compounds according to the invention.

The actual pharmaceutically effective amount or therapeutic dosage will depend on factors known by those skilled in the art such as age, weight, gender or other condition of the patient, route of administration, severity of disease, and the like.

The compounds according to the invention may be administered by oral, parenteral (intravenous, intramuscular etc.), intranasal, sublingual, inhalative, intrathecal, topical or rectal route. Suitable preparations for administering the compounds according to the present invention include for example patches, tablets, capsules, pills, pellets, dragees, powders, troches, suppositories, liquid preparations such as solutions, suspensions, emulsions, drops, syrups, elixirs, or gaseous preparations such as aerosols, sprays and the like. The content of the pharmaceutically active compound(s) should be in the range from 0.05 to 90 wt.- %, preferably 0.1 to 50 wt.-% of the composition as a whole. Suitable tablets may be obtained, for example, by mixing the active substance(s) with known excipients, for example inert diluents such as calcium carbonate, calcium phosphate or lactose, disintegrants such as corn starch or alginic acid, binders such as starch or gelatine, lubricants such as magnesium stearate or talc and/or agents for delaying release, such as carboxymethyl cellulose, cellulose acetate phthalate, or polyvinyl acetate. The tablets may also comprise several layers.

Coated tablets may be prepared accordingly by coating cores produced analogously to the tablets with substances normally used for tablet coatings, for example collidone or shellac, gum arabic, talc, titanium dioxide or sugar. To achieve delayed release or prevent incompatibilities the core may also consist of a number of layers. Similarly the tablet coating may consist of a number of layers to achieve delayed release, possibly using the excipients mentioned above for the tablets.

Syrups or elixirs containing the active substances or combinations thereof according to the invention may additionally contain a sweetener such as saccharine, cyclamate, glycerol or sugar and a flavour enhancer, e.g. a flavouring such as vanillin or orange extract. They may also contain suspension adjuvants or thickeners such as sodium carboxymethyl cellulose, wetting agents such as, for example, condensation products of fatty alcohols with ethylene oxide, or preservatives such as p-hydroxybenzoates.

Solutions are prepared in the usual way, e.g. with the addition of isotonic agents, preservatives such as p-hydroxybenzoates or stabilisers such as alkali metal salts of ethylenediaminetetraacetic acid, optionally using emulsifiers and/or dispersants, while if water is used as diluent, for example, organic solvents may optionally be used as solubilisers or dissolving aids, and the solutions may be transferred into injection vials or ampoules or infusion bottles.

Capsules containing one or more active substances or combinations of active substances may for example be prepared by mixing the active substances with inert carriers such as lactose or sorbitol and packing them into gelatine capsules.

Suitable suppositories may be made for example by mixing with carriers provided for this purpose, such as neutral fats or polyethyleneglycol or the derivatives thereof.

Excipients which may be used include, for example, water, pharmaceutically acceptable organic solvents such as paraffins (e.g. petroleum fractions), vegetable oils (e.g. groundnut or sesame oil), mono- or polyfunctional alcohols (e.g. ethanol or glycerol), carriers such as e.g. natural mineral powders (e.g. kaolins, clays, talc, chalk), synthetic mineral powders (e.g. highly dispersed silicic acid and silicates), sugars (e.g. cane sugar, lactose and glucose), emulsifiers (e.g. lignin, spent sulphite liquors, methylcellulose, starch and polyvinylpyrrolidone) and lubricants (e.g. magnesium stearate, talc, stearic acid and sodium lauryl sulphate).

For oral use the tablets may contain, in addition to the carriers specified, additives such as sodium citrate, calcium carbonate and dicalcium phosphate together with various additional substances such as starch, preferably potato starch, gelatin and

the like. Lubricants such as magnesium stearate, sodium laurylsulphate and talc may also be used to produce the tablets. In the case of aqueous suspensions the active substances may be combined with various flavour enhancers or colourings in addition to the abovementioned excipients.

The dosage of the compounds according to the invention is naturally highly dependent on the method of administration and the complaint which is being treated.

COMBINATIONS WITH OTHER ACTIVE SUBSTANCES

In another aspect the present invention relates to a combination therapy in which a compound according to the present invention is administered together with another active compound. Accordingly, the invention also refers to pharmaceutical formulations that provide such a combination of active ingredients, whereby one of which is a compound of the present invention. Such combinations may be fixed dose combinations (the active ingredients that are to be combined are subject of the same pharmaceutical formulation) or free dose combinations (active ingredients are in separate pharmaceutical formulations).

Consequently, a further aspect of the present invention refers to a combination of each of the compounds of the present invention, preferably at least one compound according to the present invention, with another compound selected from the group of for example beta-secretase inhibitors; gamma-secretase inhibitors; gamma-secretase modulators; amyloid aggregation inhibitors such as e.g. alzhemed; directly or indirectly acting neuroprotective and/or disease-modifying substances; anti-oxidants, such as e.g. vitamin E , ginko biloba or ginkolide; anti-inflammatory substances, such as e.g. Cox inhibitors, NSAIDs additionally or exclusively having Aß (Abeta) lowering properties; HMG-CoA reductase inhibitors, such as statins; acetylcholine esterase inhibitors, such as donepezil, rivastigmine, tacrine, galantamine; NMDA receptor antagonists such as e.g. memantine; AMPA receptor agonists; AMPA receptor positive modulators, AMPkines, glycine transporter 1 inhibitors; monoamine receptor reuptake inhibitors; substances modulating the concentration or release of neurotransmitters; substances inducing the secretion of growth hormone such as ibutamoren mesylate and capromorelin; CB-1 receptor

antagonists or inverse agonists; antibiotics such as minocyclin or rifampicin; PDE1, PDE2, PDE4, PDE5 and / or PDE10 inhibitors, GABAA receptor inverse agonists; GABAA receptor antagonists; nicotinic receptor agonists or partial agonists or positive modulators; alpha4beta2 nicotinic receptor agonists or partial agonists or positive modulators; alpha7 nicotinic receptor agonists or partial agonists; histamine receptor H3 antagonists; 5-HT4 receptor agonists or partial agonists; 5-HT6 receptor antagonists; alpha2-adrenoreceptor antagonists, calcium antagonists; muscarinic receptor M1 agonists or partial agonists or positive modulators; muscarinic receptor M2 antagonists; muscarinic receptor M4 antagonists; metabotropic glutamate receptor 5 positive modulators; metabotropic glutamate receptor 2 antagonists, and other substances that modulate receptors or enzymes in a manner such that the efficacy and/or safety of the compounds according to the invention is increased and/or unwanted side effects are reduced.

This invention further relates to pharmaceutical compositions containing one or more, preferably one active substance. At least one active substance is selected from the compounds according to the invention and/or the corresponding salts thereof. Preferably the composition comprises only one such active compound. In case of more than one active compound the other one can be selected from the aforementioned group of combination partners such as alzhemed, vitamin E, ginkolide, donepezil, rivastigmine, tacrine, galantamine, memantine, ibutamoren mesylate, capromorelin, minocyclin and/or rifampicin. Optionally the compositon comprises further ingreideints such as inert carriers and/or diluents.

The compounds according to the invention may also be used in combination with immunotherapies such as e.g. active immunisation with Abeta or parts thereof or passive immunisation with humanised anti-Abeta antibodies or antibodyfragments for the treatment of the above mentioned diseases and conditions.

The compounds according to the invention also may be combined with Dimebon.

The combinations according to the present invention may be provided simultaneously in one and the same dosage form, i.e. in form of a combination preparation, for

example the two components may be incorporated in one tablet, e. g. in different layers of said tablet. The combination may be also provided separately, in form of a free combination, i.e the compounds of the present invention are provided in one dosage form and one or more of the above mentioned combination partners is provided in another dosage form. These two dosage forms may be equal dosage forms, for example a co-administration of two tablets, one containing a therapeutically effective amount of the compound of the present invention and one containing a therapeutically effective amount of the above mentioned combination partner. It is also possible to combine different administration forms, if desired. Any type of suitable administration forms may be provided.

The compound according to the invention, or a physiologically acceptable salt thereof, in combination with another active substance may be used simultaneously or at staggered times, but particularly close together in time. If administered simultaneously, the two active substances are given to the patient together; if administered at staggered times the two active substances are given to the patient successively within a period of less than or equal to 12, particularly less than or equal to 6 hours.

The dosage or administration forms are not limited, in the frame of the present invention any suitable dosage form may be used. Exemplarily the dosage forms may be selected from solid preparations such as patches, tablets, capsules, pills, pellets, dragees, powders, troches, suppositories, liquid preparations such as solutions, suspensions, emulsions, drops, syrups, elixirs, or gaseous preparations such as aerosols, sprays and the like.

The dosage forms are advantageously formulated in dosage units, each dosage unit being adapted to supply a single dose of each active component being present. Depending from the administration route and dosage form the ingredients are selected accordingly.

The dosage for the above mentioned combination partners is expediently 1/5 of the normally recommended lowest dose up to 1/1 of the normally recommended dose.

The dosage forms are administered to the patient for example 1, 2, 3, or 4 times daily depending on the nature of the formulation. In case of retarding or extended release formulations or other pharmaceutical formulations, the same may be applied differently (e.g. once weekly or monthly etc.). It is preferred that the compounds of the invention be administered either three or fewer times, more preferably once or twice daily.

EXAMPLES

PHARMACEUTICAL COMPOSITIONS

Examples for illustration, without being meant to be limiting:

For illustration, pharmaceutical formulations will now be described, wherein the term "active substance" denotes one or more compounds according to the invention including the salts thereof. In the case of one of the aforementioned combinations with one or more other active substances the term "active substance" may also include the additional active substances.

Example A

Tablets containing 100 mg of active substance

Composition: tablet

active substance	100.0 mg
lactose	80.0 mg
corn starch	34.0 mg
polyvinylpyrrolidone	4.0 mg
magnesium stearate	2.0 mg
	220.0 mg

Example B

Tablets containing 150 mg of active substance

Composition: tablet

active substance	150.0 mg
powdered lactose	89.0 mg
corn starch	40.0 mg
colloidal silica	10.0 mg
polyvinylpyrrolidone	10.0 mg
magnesium stearate	1.0 mg
	300.0 mg

Example C

Hard gelatine capsules containing 150 mg of active substance

Compostion: capsule

active substance		150.0 mg
corn starch (dried)	approx.	80.0 mg
lactose	approx.	87.0 mg
magnesium stearate		3.0 mg
	approx.	320.0 mg

Example D

Composition: suppository

active substance	150.0 mg
polyethyleneglycol 1500	550.0 mg

polyethyleneglycol 6000	460.0 mg
polyoxyethylene sorbitan monostearate	840.0 mg
	2,000.0 mg

Example E

Composition: ampoules containing 10 mg active substance

active substance		10.0 mg
0.01 N hydrochloric acid q.s.		
double-distilled water	ad	2.0 mL

Example F

Composition: ampoules containing 50 mg of active substance

active substance		50.0 mg
0.01 N hydrochloric acid q.s.		
double-distilled water	ad	10.0 mL

The preparation of any the above mentioned formulations can be done following standard procedures.

BIOLOGICAL ASSAY

The in vitro effect of the compounds of the invention can be shown with the following biological assays.

PDE9A2 assay protocol:

The PDE9A2 enzymatic activity assay was run as scintillation proximity assay (SPA), in general according to the protocol of the manufacturer (GE Healthcare, former Amersham Biosciences, product number: TRKQ 7100).

As enzyme source, lysate (PBS with 1 % Triton X-100 supplemented with protease inhibitors, cell debris removed by centrifugation at 13.000 rpm for 30 min) of SF 9 cell expressing the human PDE9A2 was used. The total protein amount included in the assay varied upon infection and production efficacy of the SF9 cells and lay in the range of 0.1 – 100 ng.

In general, the assay conditions were as follows:

- total assay volume: 40 microliter
- protein amount: 0.1 – 50 ng
- substrate concentration (cGMP): 20 nanomolar; ~1 mCi/l
- incubation time: 60 min at room temperature
- final DMSO concentration: 0.2 - 1 %

The assays were run in 384-well format. The test reagents as well as the enzyme and the substrate were diluted in assay buffer. The assay buffer contained 50 mM Tris, 8.3 mM $MgCl_2$, 1.7 mM EGTA, 0.1 % BSA, 0.05 % Tween 20; the pH of assay buffer was adjusted to 7.5. The reaction was stopped by applying a PDE9 specific inhibitor (e.g. compounds according to WO04099210 or WO04099211, like one of the enantiomeres of example 37, e.g. 1-(2-Chlorophenyl)-6-[(2R)-3,3,3-trifluoro-2-methyl-propyl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidine-4-one) in excess.

References:

Wunder F, Tersteegen A, Rebmann A, Erb C, Fahrig T, Hendrix M. Characterization of the first potent and selective PDE9 inhibitor using a cGMP reporter cell line. *Molecular Pharmacology*. 2005 Dec;68(6):1775-81.

van der Staay FJ, Rutten K, Bärfacker L, Devry J, Erb C, Heckroth H, Karthaus D, Tersteegen A, van Kampen M, Blokland A, Prickaerts J, Reymann KG, Schröder UH, Hendrix M. The novel selective PDE9 inhibitor BAY 73-6691 improves learning and memory in rodents. *Neuropharmacology*. 2008 Oct;55(5):908-18.

<u>PDE1C assay protocol:</u>

The assay was run in an analogue manner as the PDE9A2 assay, with the following differences: instead of PDE9A2 PDE1C has been used and the assay buffer contained in addition 50 nM Calmodulin, 3 mM $CaCl_2$. The reaction can be stopped by applying the same inhibitor than the one that is outlined above (1-(2-Chlorophenyl)-6-[(2R)-3,3,3-trifluoro-2-methyl-propyl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidine-4-one).

Determination of % inhibition:

The activity of the positive control (minus the negative control = background) is set to 100 % and activity in the presence of test compound is expressed relative to these 100 %. Within this setting, an inhibition above 100 % might be possible due to the nature of the variation of the positive control within the assay. In the following inhibition of PDE9A2 is presented for a concentration at 10 µM, if not indicated otherwise.

Determination of IC_{50}:

IC_{50} can be calculated with GraphPadPrism or other suited software setting the positive control as 100 and the negative control as 0. For calculation of IC_{50} dilutions of the test compounds (substrates) are to be selected and tested following the aforementioned protocol.

Data

In the following, % inhibition (%I) data at 10 micromolar concentration (at 10 microM) and IC_{50} values for PDE9A2 inhibition [nanomolar (nM)] will illustrate that the compounds according to the present invention are suited to inhibit PDE9, specifically PDE9A2. This evidences that the compounds provide useful pharmacological properties (Tabe 4). The examples are not meant to be limiting.

Within this setting, an inhibition above 100% might be possible due to the nature of the variation of the positive control within the assay.

The table also provides selectivity values (S) that show a preference of the compounds for PDE9A versus PD1C. Selectivity is the ratio (IC_{50} for PDE1C inhibition) / (IC_{50} for PDE9A2 inhibition).

The example numbers refer to the final examples as outlined in the section "**Exemplary embodiments**".

All data are measured according to the procedure described herein.

Table 4

I% (at 10 microM): inhibition at 10 micromolar concentration.

IC_{50} (nM): IC_{50} values for PDE9A2 inhibition [nanomolar (nM)]

S: selectivity values [= (IC_{50} for PDE1C inhibition) / (IC_{50} for PDE9A2 inhibition)]

Example No.	I% (at 10 microM)	IC_{50} (nM)	S
219	103	12	179
220	104	5	526
221	103	6	98
222	104	15	131
223	100	5	1717
224	100	12	146
225	102	6	290
226	101	9	225
227	101	8	147
228	101	6	244
229	99	14	135
230	101	12	145
230-1	98	5	197
230-2	102	5	286
230-3	99	11	135
230-5	98	6	274

Example No.	I% (at 10 microM)	IC_{50} (nM)	S
231	95	18	245
232	99	7	255
234	101	3	> 3333
239	92	2	400
240	100	5	126
241	100	6	368
242	96	23	> 429
243	96	18	114
244	99	26	110
245	95	21	22
246	94	55	17
247	98	27	42
248	97	45	28
249	101	28	68
250	99	24	184
251	101	38	27

Example No.	I% (at 10 microM)	IC_{50} (nM)	S
252	96	11	493
253	99	34	56
254	97	20	238
255	101	41	12
256	103	5	123
257	103	31	10

Example No.	I% (at 10 microM)	IC_{50} (nM)	S
258	100	7	122
259	102	3	942
260	103	7	266
261	102	4	580
262	101	20	451
263	102	8	1116

In vivo effect:

The in vivo effect of the compounds of this invention can be tested in the Novel Object Recognition test according to the procedure of Prickaerts *et al.* (*Neuroscience* **2002**, *113*, 351-361) or T-maze spontaneous alternation test according to the procedures described by van der Staay *et al.* (*Neuropharmacology* **2008**, 55, 908-918). For further information concerning biological testing it is also referred to these two citations.

Beside the inhibition property toward the target PDE9, compounds according to the present invention may provide further pharmacokinetic properties of advantage.

E.g. compounds according to the invention may show one or more advantages in the area of balanced metabolism, low risk of causing drug - drug interaction and/or balanced clearance.

Compounds also might show one or more additional or alternative advantages in the area of bioavailability, high fraction absorbed, blood brain transport properties, a favourable (e.g. high mean) residence time (mrt), favourable exposure in the effect compartment and so on.

CHEMICAL MANUFACTURE

In this section, compounds according to the invention will be disclosed as well as chemically similar compounds that do not show the exact motif as defined for R^1. The way of manufacture for both types of compounds will illustrate the manufacturing method for the compounds according to the invention.

Abbreviations:

APCI	*Atmospheric pressure chemical ionization*
DAD	*diode array detector*
DMSO	*dimethyl sulphoxide*
ESI	*electrospray ionization (in MS)*
Exp.	*example*
Fp.	*melting point*
h	*hour(s)*
HPLC	*high performance liquid chromatography*
HPLC-MS	*coupled high performance liquid chromatography with mass spectrometric detection*
GC-MS	*gas chromatography with mass spectrometric detection*
MPLC	*medium pressure liquid chromatography*
mL	*millilitre*
µL	*microlitre*
min	*minutes*
MS	*mass spectrometry*
racem.	*racemic*
rt	*room temperature*
R_t	*retention time (in HPLC)*
Rf	*retardation factor (in TLC)*
TBTU	*2-(1 H-Benzotriazole-1-yl)-1,1,3,3-Tetramethyluronium tetrafluoroborate*
TFA	*trifluoroacetic acid*
TLC	*thin-layer chromatography*

LC-MS methods:

Method A

Instrument: HPLC/MS ThermoFinnigan. HPLC Surveyor DAD, LCQduo Ion trap.; column: Sunryse MS-C18, 5 um, 4.6x100 mm; eluent A: water + 20 mM ammonium formate; eluent B: acetonitrile + 20 mM ammonium formate; gradient: A/B (95:5) for 1 min, then to A/B (5:95) in 7 min for 1.5 min; flow rate: 0.85 mL/min; UV detection: 254 nm; ion source: ESI

Method 1

MS apparatus type: Waters Micromass ZQ; HPLC apparatus type: Waters Alliance 2695, Waters 2996 diode array detector; column: Varian Microsorb 100 C18, 30 x 4.6 mm, 3.0 μm; eluent A: water + 0.13 % TFA, eluent B: acetonitrile; gradient: 0.0 min 5 % B → 0.18 min 5 % B → 2.0 min 98 % B → 2.2 min 98 % B → 2.3 min 5 % B → 2.5 min 5 % B; flow rate: 3.5 mL/min; UV detection: 210-380 nm.

Method 2

MS apparatus type: Waters Micromass ZQ; HPLC apparatus type: Waters Alliance 2695, Waters 2996 diode array detector; column: Merck Chromolith Performance RP18e, 100 x 1 mm; eluent A: water + 0.13 % TFA, eluent B: acetonitrile; gradient: 0.0 min 5 % B → 0.2 min 5 % B → 1.6 min 98 % B → 1.9 min 98 % B → 2.0 min 5 % B → 2.2 min 5 % B; flow rate: 3.5 mL/min; UV detection: 210-380 nm.

Method 1D

Instrument:HPLC-MS ThermoFinnigan. HPLC Surveyor DAD, MSQ Quadrupole; column: Sunryse MS-C18, 5 um, 4.6 x 100 mm; eluent A: 90 % water +10 % acetonitrile + ammonium formate 10 mM; eluent B: acetonitrile 90 % + 10 % water + ammonium formate 10 mM; gradient:A (100) for 1 min, then to B (100) in 7 min for 1 min; flow rate: 1.2 mL/min; UV detection: 254 nm; ion source: APCI.

Method 1E

Instrument: HPLC-MS ThermoFinnigan. HPLC Surveyor DAD, MSQ Quadrupole; column: Symmetry C8, 5 μm, 3 x 150 mm; eluent A: 90 % water + 10 % acetonitrile + ammonium formate 10 mM; eluent B: acetonitrile 90 % + 10 % H_2O + ammonium formate 10 mM; gradient: A (100) for 1.5 min, then to B (100) in 10 min for 1.5 min; flow rate: 1.2 mL/min; UV detection: 254 nm; ion source: APCI

Method 1E fusion

Instrument: HPLC-MS ThermoFinnigan. HPLC Surveyor DAD, MSQ Quadrupole; column: Synergi Fusion-RP80A, 4 µm, 4.60 x 100 mm; eluent A: 90 % water + 10 % acetonitrile + ammonium formate 10mM; eluent B: acetonitrile 90 % + 10 % H_2O + ammonium formate 10 mM; gradient: A (100 %) for 1.5 min, then to B (100 %) in 10 min for 1.5 min; flow rate: 1.2 mL/min; UV detection: 254 nm; ion source: APCI

Method 1E hydro

Instrument: HPLC-MS ThermoFinnigan. HPLC Surveyor DAD, MSQ Quadrupole; column: Synergi Hydro-RP80A, 4 µm, 4.60 x 100 mm; eluent A: 90 % water + 10 % acetonitrile + ammonium formate 10 mM; eluent B: acetonitrile 90 % + 10 % H_2O + ammonium formate 10 mM; gradient: A (100 %) for 1.5 min, then to B (100 %) in 10 min for 1.5 min; flow rate: 1.2 mL/min; UV detection: 254 nm; ion source: APCI

Method 2F

Instrument: HPLC-MS ThermoFinnigan. HPLC Surveyor DAD, Finnigan LCQduo Ion trap; column: Symmetry-C18, 5 um, 3 x 150 mm; eluent A: 95 % water + 5 % acetonitrile + formic acid 0.1 %; eluent B: acetonitrile 95 % + 5 % water + formic acid 0.1 %; gradient: A/B (95/5) for 1.5 min, then to A/B (5/95) in 10 min for 1.5 min; flow rate: 1 mL/min; UV detection: 254 nm; ion source: ESI

Method 2L

Instrument: HPLC-MS ThermoFinnigan. HPLC Surveyor DAD, Finnigan LCQduo Ion trap;
column: Symmetry Shield, 5 um, 4,6 x 150 mm; eluent A: 90 % water + 10 % acetonitrile + formic acid 0.1 %; eluent B: acetonitrile 90 % + 10 % water + formic acid 0.1 %; gradient: A/B (70/30) in 1.5 min to A/B (50/50) then to B (100%) in 7 min and for 9.5 min; flow rate: 0,85 mL/min; UV detection: 254 nm; ion source: ESI

Method 2M

Instrument: HPLC-MS ThermoFinnigan. HPLC Surveyor DAD, Finnigan LCQduo Ion trap;
column: Symmetry Shield, 5 um, 4,6 x 150 mm; eluent A: 90 % water + 10 % acetonitrile + formic acid 0.1 %; eluent B: acetonitrile 90 % + 10 % water + formic acid 0.1 %; gradient: A/B (90/10) for 1.5 min, then to A/B (5/95) in 10 min for 2 min; flow rate: 1,2 mL/min; UV detection: 254 nm; ion source:APCI

Method Grad_C8_acidic

Instrument: HPLC-MS Waters. HPLC Alliance 2695 DAD, ZQ Quadrupole; column: Xterra MS-C8, 3.5 µm, 4.6 x 50 mm; eluent A: water + 0.1 % TFA + 10 % acetonitrile; eluent B: acetonitrile; gradient: A/B (80:20), then to A/B (10:90) in 3.25 min for 0.75 min; flow rate: 1.3 mL/min; UV detection: 254 nm; ion source: ESI

Method Grad_C18_acidic

Instrument: HPLC-MS Waters. HPLC Alliance 2695 DAD, ZQ Quadrupole; column: Sunfire MS-C18, 3.5 µm, 4.6 x 50 mm; eluent A: water + 0.1 % TFA + 10 % acetonitrile; eluent B: acetonitrile; gradient: A/B (80:20), then to A/B (10:90) in 3.25 min for 0.75 min; flow rate:1.3 mL/min; UV detection: 254 nm; ion source: ESI.

Method Grad_90_10_C8_acidic

Instrument: HPLC-MS Waters. HPLC Alliance 2695 DAD, ZQ Quadrupole; column: Xterra MS-C8, 3.5 µm, 4.6 x 50 mm; eluent A: water + 0.1 % TFA + 10 % acetonitrile; eluent B: acetonitrile; gradient: A (100 %), then to A/B (10:90) in 3.25 min for 0.75 min; flow rate: 1.3 mL/min; UV detection: 254 nm; ion source: ESI.

Method Grad_90_10_C18_acidic

Instrument: HPLC-MS Waters. HPLC Alliance 2695 DAD, ZQ Quadrupole; column: Xterra MS-C18, 3.5 µm, 4.6 x 50 mm; eluent A: water + 0.1 % TFA + 10 % acetonitrile; eluent B: acetonitrile; gradient: A (100), then to A/B (10:90) in 3.25 min for 0.75 min; flow rate:1.3 mL/min; UV detection: 254 nm; ion source: ESI.

Method Grad_C8_NH_4COOH

Instrument: HPLC-MS Waters. HPLC Alliance 2695 DAD, ZQ Quadrupole. Column: Xterra MS-C8, 3.5 µm, 4.6 x 50 mm; eluent A: water + ammonium formate 5 mM + 10 % acetonitrile; eluent B: acetonitrile; gradient: A 100 %, then to A/B (10:90) in 3.25 min for 0.75 min; flow rate: 1.3 mL/min; UV detection: 254 nm; ion source: ESI.

Method 5

MS apparatus type: Waters Micromass ZQ; HPLC apparatus type: Waters Alliance 2695, Waters 2996 diode array detector; column: Varian Microsorb 100 C18, 30 x 4.6 mm, 5.0 µm; eluent A: water + 0.15 % TFA, eluent B: methanol; gradient: 0.0 min 5 % B → 0.15 min 5 % B → 2.55 min 100 % B → 2.70 min 100 % B → 2.80 min 5 % B → 3.05 min 5 % B; flow rate: 4.8 mL/min; UV detection: 210-400 nm.

Method 6

MS apparatus type: Waters Micromass ZQ; HPLC apparatus type: Waters Alliance 2695, Waters 2996 diode array detector; column: Waters Sunfire C18, 20 x 4.6 mm, 5.0 µm; eluent A: water + 0.15 % TFA, eluent B: methanol; gradient: 0.0 min 5 % B → 0.25 min 5 % B → 1.90 min 100 % B → 2.05 min 100 % B → 2.15 min 5 % B → 2.30 min 5 % B; flow rate: 5.2 mL/min; UV detection: 210-400 nm.

Method 7

MS apparatus type: Waters Micromass ZQ; HPLC apparatus type: Waters Alliance 2695, Waters 2996 diode array detector; column: Waters Varian Microsorb C18, 20 x 4.6 mm, 5.0 µm; eluent A: water + 0.15 % TFA, eluent B: methanol; gradient: 0.0 min 5 % B → 0.25 min 5 % B → 1.90 min 100 % B → 2.05 min 100 % B → 2.15 min 5 % B → 2.30 min 5 % B; flow rate: 5.2 mL/min; UV detection: 210-400 nm.

Chiral HPLC Methods

Instrument: Agilent 1100. Column: Chiralpak AS-H Daicel, 4.6 µm, 4.6 x 250 mm;

Method Chiral 1: eluent: hexane/ethanol 97/3 (isocratic); flow rate: 1.0 mL/min; UV detection: 254 nm.

Method Chiral 2: eluent: hexane/ethanol 98/2 (isocratic); flow rate: 1.0 mL/min; UV detection: 254 nm

Method Chiral 3: eluent: hexane/ethanol 80/20 (isocratic); flow rate: 1.0 mL/min; UV detection: 254 nm

GC/MS methods

Method 3A

Instrument: GC/MS Finnigan. Trace GC, MSQ quadrupole. Column: DB-5MS, 25 m x 0.25 mm x 0.25 µm; carrier gas: helium, 1 mL/min constant flow; oven program: 50°C (hold 1 minute), to 100°C in 10°C/min, to 200°C in 20°C/min, to 300°C in 30°C/min eluent, detection: trace MSQ, quadrupole

ion source: IE scan range: 50-450 u.

Method 3A.1

Instrument: GC/MS Finnigan Thermo Scientific. Trace GC Ultra, DSQ II single quadrupole. Column: DB-5MS UI, 25 m x 0.25 mm x 0.25 µm; carrier gas: helium, 1 mL/min constant flow; oven program: 50°C (hold 1 minute), to 100°C in 10°C/min, to 200°C in 20°C/min, to 300°C in 30°C/min eluent, detection: trace DSQ, single quadrupole

Microwave heating:

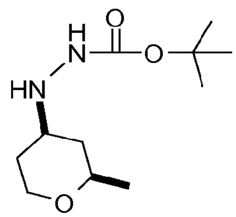
Microwave apparatus types:

- Discover® CEM instruments, equipped with 10 and 35 mL vessels;
- Microwave apparatus type: Biotage Initiator Sixty.

<u>General comment concerning the presentation of the structures</u>

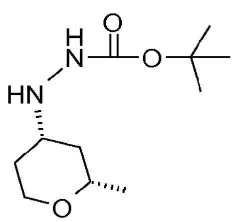
Some compounds have one or more chiral centres. The depicted structure will not necessarily show all the possible stereochemical realisation of the compound but only one. However, in such cases a term like “cis-racemic mixture” is depicted next to the structure in order to point to the other stereochemical options.

An example is given for Example 7D, below. The presented structural formula is



Cis - racemic mixture

The added term “cis - racemic mixture” points to the second stereochemical option:



This principle applies to other depicted structures as well.

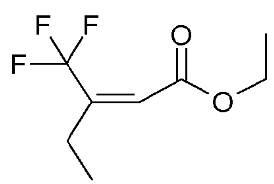
Synthesis

In the following the manufacture of compounds which exemplify the present invention is described. In case the process of manufacture of a specific compound has not been disclosed literally, the skilled person in the art will find a description of analogue procedures within these descriptions which he can follow in principle. At some places it is said, the examples can be prepared in analogy to another example. If reference should be made to such an “analogue process” the reactions conditions are about

the same, even if molar ratios of reagents and educts might to be adjusted. It also will be evident that starting materials within a described process can be varied chemically to achieve the same results, i.e. if a condensation reaction of an ester is described, in that the alcoholic component is a leaving group but not subject of the product, this alcoholic component may vary without significant changes of the procedure as such.

Starting compounds:

Example 1A

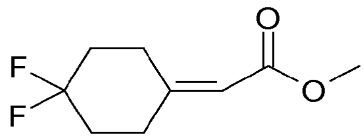


A solution of 70 g (201 mmol) carbethoxymethylene triphenylphosphorane in 300 mL diethyl ether was cooled to 0°C and 25 g (198 mmol) 1.,1,1-trifluorobutanone was added. The solution was warmed to room temperature and stirred over night. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure (700 mbar and 40°C bath temperature). The residue was purified by vacuum distillation (170 mbar and 130°C bath temperature, main fraction: 95-96°C). 29 g (75 %) of the product were obtained as colourless oil.

HPLC-MS (Method 1): R_t: 1.77 min

MS (ESI pos): m/z = 196 $(M+H)^+$

Example 1AA



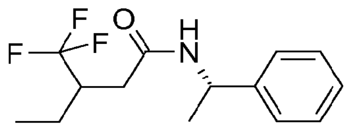
400 mg (10.0 mmol) sodium hydride (60 % in mineral oil) was suspended in 10 ml THF and cooled to 4°C. While being stirred, a solution of 1.3 ml (8.99 mmol) trimethylphosphono acetate in 10 ml THF was added. The mixture was stirred for 1 h at the same temperature. After this, a solution of 4,4-difluorocyclohexanone in 10 ml THF was added at 0°C. The mixture was allowed to warm to room temperature and stirred for 14 h. THF and water was added and the THF evaporated. The remainder was diluted with ethyl acetate, washed with water and saturated sodium hydrogen carbonate solution and evaporated to yield 1.49 g (95 %) of the product.

MS (EI): m/z = 190 $(M)^+$

The following examples 1B, 1C, 1D, 1E, 2A, 2B, 2C and 2D show how the racemic acids 3-trifluoromethyl-pentanoic acid and 3-trifluoromethyl-butyric acid can be transferred into the two enantiomeric forms of the free acid. The resolution can be done via separation of diastereomeric intermediates. The two pure enantiomeric forms of the free acid will be called enantiomer A, enantiomer B respectively. The corresponding diastereomeric intermediates will be called diastereomer A, diastereomer B respectively.

The same principle may be applied for enantiomeric resolution of other racemic mixtures if appropriate.

<u>Example 1B</u>



Diastereoisomer A

A solution of racemic 3-trifluoromethyl-pentanoic acid (8 g, 47 mmol), TBTU (16.6 g, 52 mmol) and diisopropylethylamine (24.1 mL, 141 mmol) in dimethylformamide (80 mL) was stirred at 20°C for 1h then (*S*)-(−)-1-phenylethylamine (10 g, 82 mmol) was added and the mixture was stirred for 16 h at 20°C. The solvent was removed and dichloromethane (200 mL) was added. The resulting mixture was washed with citric acid 10 % in water (200 mL), K_2CO_3 20 % in water (100 mL) and dried over sodium sulphate. Evaporation of the solvent gave a crude solid that was mixed with methanol (10 mL) and filtered through a pad of activated basic alumina. Separation of diastereoisomers was obtained by flash chromatography on SiO_2 eluting with a mixture of cyclohexane/ethyl acetate 85/15.

4.5 g (35.8 %) of the title compound were obtained as white solid.

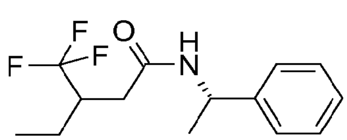
Rf: 0.25 (cyclohexane/ethyl acetate 85/15, stained with basic $KMnO_4$)

HPLC-MS (Method 1E hydro): R_t: 9.35 min

MS (APCI pos): m/z = 274 $(M+H)^+$.

Chiral HPLC (Method Chiral 1): R_t: 5.58 min de: >99 %

<u>Example 1C</u>



Diastereoisomer B

4.4 g (34.2 %) of a white solid were obtained as second product from flash chromatography of Example 1B.

Rf: 0.20 (cyclohexane/ethyl acetate 85/15, stained with basic $KMnO_4$)

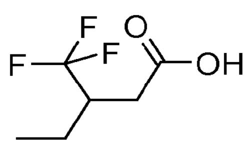
HPLC-MS (Method 1E hydro): R_t: 9.33 min

MS (APCI pos): m/z = 274 $(M+H)^+$.

Chiral HPLC (Method Chiral 1): R_t: 6.18 min de: >99 %

Example 1D

3-Trifluoromethyl-pentanoic acid, Enantiomer A



Enantiomer A

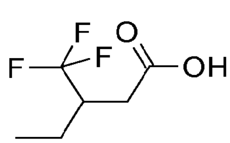
A solution of Example 1B (4.6 g, 17 mmol) in dioxane (15 mL) was treated with H_2SO_4 70 % in water (25 mL) and refluxed for 16 h. The mixture was cooled, basified to pH 14 with NaOH 32 % in water, diluted with water (50 mL) and extracted with dichloromethane (2x 200 mL). The resulting solution was acidified to pH 1 with 9N HCl, extracted with dichloromethane (3x 500 mL) and the combined organic phases were dried. Evaporation of solvent afforded 2.47 g (86.3 %) of a brown oil.

Rf: 0.66 (dichloromethane/methanol 9/1, stained with Bromocresol Green)

Chiral HPLC (Method Chiral 1): R_t 5.58 min ee: >99 %

Example 1E

3-Trifluoromethyl-pentanoic acid, Enantiomer B



Enantiomer B

In analogy to the preparation of Example 1D, the title compound was obtained using Example 1C as starting material.

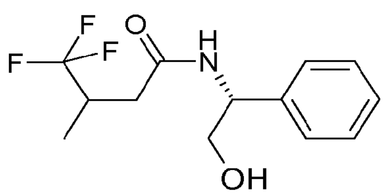
Yield: 80.3 %

Rf: 0.66 (dichloromethane/methanol 9/1, stained with Bromocresol Green)

Chiral HPLC (Method Chiral 1): R_t: 5.08 min ee: >99 %

Example 2A

4,4,4-Trifluoro-N-((R)-2-hydroxy-1-phenyl-ethyl)-3-methyl-butyramide, Diastereoisomer A



A solution of 3-(trifluoromethyl)butyric acid (10 g, 64 mmol) in dimethylformamide (100mL) was treated with N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (14.7 g, 77 mmol), 4-dimethyl-amino pyridine (11 g, 89.7 mmol) and (R)-(-)-phenylglycinol (9.9 g, 70.5 mmol). The mixture was stirred at 20°C for 16h, then concentrated to reduce the volume and treated with 10 % citric acid in water (300 mL). The mixture was extracted with ethyl ether (2x 200mL) and the separated organic phase were washed with 10 % $NaHCO_3$ (150 mL) and brine (150 mL). The organic phase was dried and evaporated to give 13.1 g of a crude white solid.

Separation of diastereoisomers was achieved by flash chromatography on SiO_2 eluting with a mixture of ethyl acetate/hexane 6/4.

5.32g (30.2 %) of the title compound were obtained as white solid.

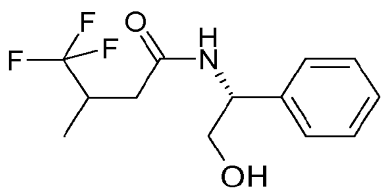
Rf: 0.23 (ethyl acetate/hexane 6/4)

HPLC-MS (1E hydro): R_t: 6.97 min

MS (APCI pos): m/z = 276 $(M+H)^+$.

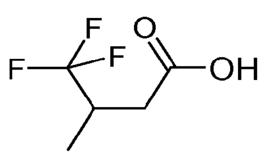
Example 2B

4,4,4-Trifluoro-N-((R)-2-hydroxy-1-phenyl-ethyl)-3-methyl-butyramide, Diastereoisomer B



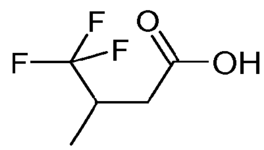
3.08 g (17.5 %) of a white solid were obtained as second product from flash chromatography of Example 2A.
Rf: 0.16 (ethyl acetate/hexane 6/4)
HPLC-MS (1E hydro): R_t: 6.92 min
MS (APCI pos): m/z = 276 $(M+H)^+$.

Example 2C, Enantiomer A



A solution of Example 2A (2 g, 7.26 mmol) in tetrahydrofuran (10 mL) was treated with H_2SO_4 70 % in water (10 mL) and refluxed for 16 h. The mixture was cooled, basified to pH 14 with NaOH 32 % in water, diluted with water (50 mL) and extracted with dichloromethane (2x 50mL). The resulting solution was acidified to pH 1 with 9N HCl, extracted with dichloromethane (3x 50 mL) and the combined organic phases were dried. Evaporation of solvent afforded 0.84 g (74.1 %) of a brown oil.
HPLC-MS (1E hydro): R_t: 1.73 min
MS (APCI neg): m/z = 155 $(M-H)^-$.
Chiral HPLC (Method Chiral 2): R_t: 6.92 min ee: 99 %

Example 2D, Enantiomer B



In analogy to the preparation of Example 2C, the title compound was obtained using Example 2B as starting material. Obtained 1.4 g (8.96 mmol)

Yield: 82.3 %

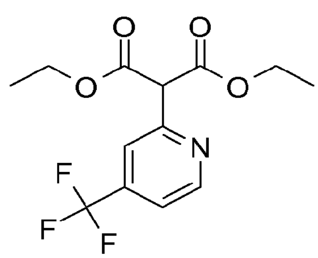
HPLC-MS (1E hydro): R_t: 1.30 min

MS (APCI neg): m/z = 155 $(M-H)^-$.

Chiral HPLC (Method Chiral 2): R_t: 6.49 min ee: 98.6 %

Example 3A

2-(4-Trifluoromethyl-pyridin-2-yl)-malonic acid diethyl ester



A suspension of sodium hydride 60 % in mineral oil (1.65 g, 41 mmol) in anhydrous dioxane (36 mL) was treated with diethylmalonate (6.3 mL, 41 mmol) at 25°C and heated to 60°C for 30 min. Cuprous chloride (1.63 g, 17 mmol) was added, the mixture was heated to 80°C and 2-chloro-4-(trifluoromethyl)-pyridine was added and the was heating increased to 100°C for 16h.

After cooling to 20°C the mixture was acidified with 37 % HCl, diluted with water (120 mL) and extracted with dichloromethane (2 x 60 mL). The organic phase was dried and evaporated to give a crude oil that was purified by flash chromatography eluting with n-hexane/ethyl acetate from 95/5 to 60/40.

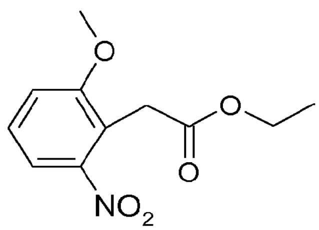
1.9 g (38 %) were obtained as a colourless oil.

HPLC-MS (2F): R_t: 12.24 min

MS (ESI pos): m/z = 306 $(M+H)^+$.

Example 4A

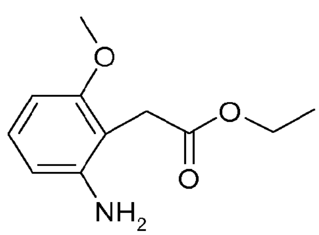
The following example was synthesized in analogy to the preparation of Example 5U, using the corresponding acid (Sinova Inc., Bethesda, MD 20814, USA) as starting material.



HPLC-MS (Method 1): R_t: 1.47 min

MS (ESI pos): m/z = 194 $(M+H-EtOH)^+$

Example 4B



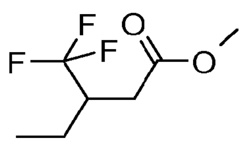
2.0 g (8.6 mmol) of Example 4A was dissolved in 40 mL ethanol, Pd (10 % on charcoal) was added, and the mixture was hydrogenated at room temperature (2h, 50 psi). The reaction mixture was filtered and the residue washed with ethanol. The

solvent was evaporated by reduced pressure.1.80 g (100 %) of the product were obtained.

HPLC-MS (Method 1): R_t: 0.91 min
MS (ESI pos): m/z = 210 $(M+H)^+$

Example 5A

3-Trifluoromethyl-pentanoic acid methyl ester, Enantiomer A



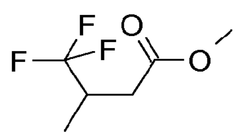
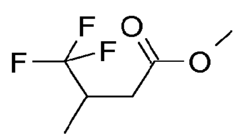
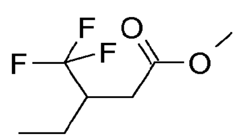
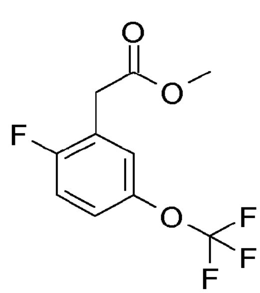
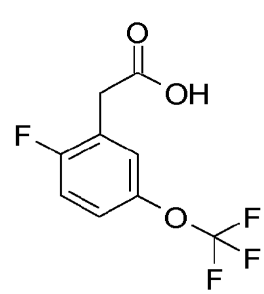
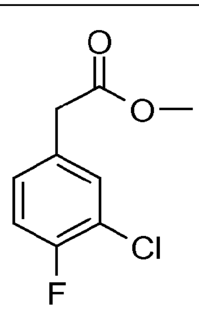
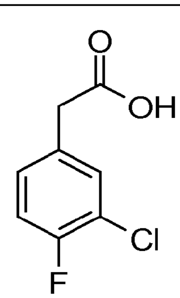
Enantiomer A

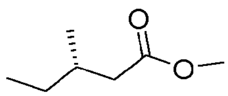
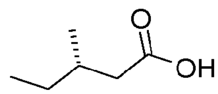
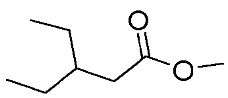
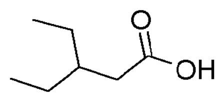
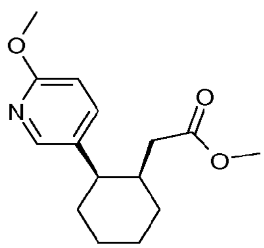
To a stirred solution of Example 1D (250 mg, 1.47 mmol) in dichloromethane (10 mL) and methanol (0.25 mL), under nitrogen atmosphere, trimethylsilyldiazomethane (2.0 M solution in diethyl ether) (2.1 mL, 4.19 mmol) was added drop wise at 0°C. The reaction mixture was stirred keeping the temperature below 5°C for 1h. The solvent was removed (40°C, 25 bar) yielding 250 mg (75.4 %) of a yellow oil that was used in the next step without further purification.

GC (Method 3A): R_t: 3.29 min
MS (EI): m/z: 165 $(M-19)^+$,155 $(M-29)^+$, 153 $(M-31)^+$

The following examples were synthesized in analogy to the preparation of Example 5A, using the corresponding acids as starting materials:

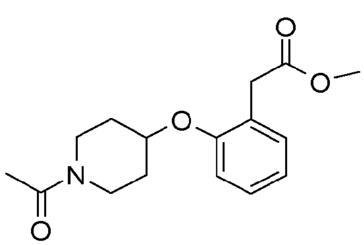
	structure	starting material: carboxylic acid	R_t [min]	MS *m/z*

	structure	starting material: carboxylic acid	R_t [min]	MS *m/z*
Example 5B Enantiomer A		Example 2C	8.01 (Method 3A)	170 [EI]
Example 5 C Enantiomer B		Example 2D	8.01 (Method 3A)	170 [EI]
Example 5D Enantiomer B		Example 1E	3.29 (Method 3A)	$165(M-19)^+$, $155(M-29)^+$, $153(M-31)^+$ [EI]
Example 5E			7.82 (Method 3A)	252 [EI]
Example 5F			9.53 (Method 3A)	202 [EI]

	structure	starting material: carboxylic acid	R_t [min]	MS *m/z*
Example 5G Enantio-mer S			3.92 (Method 3A)	130 [EI]
Example 5H			5.09 Method 3A	115 $(M-29)^{\pm}$ [EI]
Example 5HA cis, racem. mixture		Example 18A	1.22 (Method 1)	264 [ESI, $(M+H)^{+}$]

<u>Example 5I</u>

[2-(1-Acetyl-piperidin-4-yloxy)-phenyl]-acetic acid methyl ester



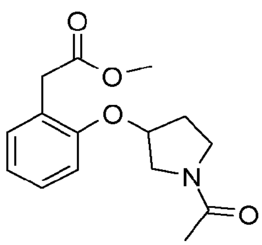
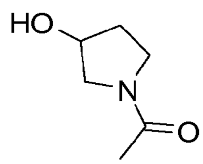
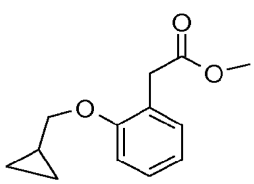
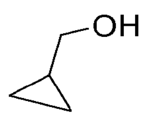
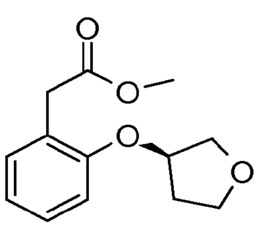
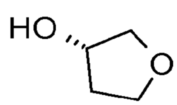
Di-tert-butylazodicarboxylate (305 mg, 1.32 mmol) was dropped to a solution of 1-(4-hydroxy-piperidin-1-yl)-ethanone (259 mg, 1.8 mmol) in tetrahydrofuran (4 mL) under nitrogen atmosphere. Then (2-hydroxy-phenyl)-acetic acid methyl ester (200 mg, 1.2

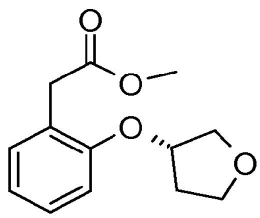
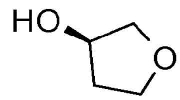
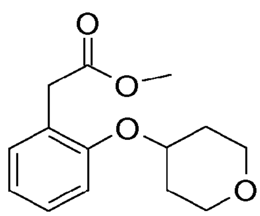
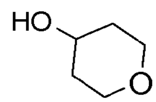
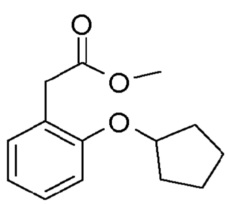
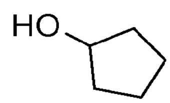
mmol) and triphenylphosphine (347 mg, 1.3 mmol) were added. The yellow mixture was stirred at 20°C for 16h. The solvent was evaporated and the residue was purified on silica using hexane/ethyl acetate mixture of increasing polarity (from 70 % to 100 % ethyl acetate) as eluent to give 195 mg (55.6 %) of a colourless oil.

HPLC-MS (Method Grad_C8_NH_4COOH): R_t: 2.67 min

MS (ESI pos): m/z = 292 $(M+H)^+$.

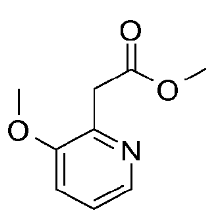
The following examples were synthesized in analogy to the preparation of Example 5G, using the corresponding alcohols as starting materials:

	Structure	starting material: Alcohol	Rf	R_t [min]	MS m/z
Example 5J racem. mixture				2.53 (Method Grad_C8_ NH_4COOH)	292 $(M+H)^+$
Example 5K			0.35 (hexane/ethyl acetate 8/2)		
Example 5L			0.2 (hexane/ethyl acetate 7/3)		

	Structure	starting material: Alcohol	Rf	R_t [min]	MS m/z
Example 5M			0.2 (hexane/ethyl acetate 7/3)		
Example 5O			0.25 (hexane/ethyl acetate 7/3)		
Example 5P			0.35 (hexane/ethyl acetate)		

<u>Example 5Q</u>

(3-Methoxy-pyridin-2-yl)-acetic acid methyl ester



A mixture of (3-methoxy-2-pyridin-2-yl) acetonitrile (400 mg, 2.7 mmol) in 2 mL of methanol and 96 % sulphuric acid (1.8 mL, 32 mmol) was heated in a microwave

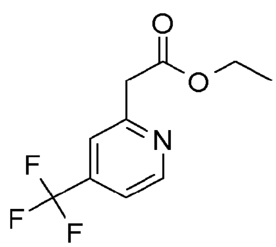
oven at 120°C for 1h. The mixture was cooled to 0°C, basified with solid $NaHCO_3$, diluted with water (2mL) and extracted with dichloromethane. The separated organic phase was dried and evaporated to give 450 mg (92 %) of a dark yellow oil that was used in the next step without further purification.

HPLC-MS (Method Grad_C8_NH_4COOH): R_t: 1.92 min

MS (ESI pos): m/z = 182 $(M+H)^+$.

Example 5R

(4-Trifluoromethyl-pyridin-2-yl)-acetic acid ethyl ester



A solution of Example 3A (1.0 g, 3.27 mmol) in anhydrous DMSO (8 mL) was treated with water (60 microL, 3.27 mmol) and lithium chloride (347 mg, 8.2 mmol). The resulting mixture was heated at 120°C for 16h. After cooling to 20°C the mixture was treated with brine (12 mL) and extracted with ethyl acetate (3x 20 mL). The organic phase was dried and evaporated to give a crude oil that was purified by flash chromatography eluting with n-hexane/ethyl acetate 8/2.

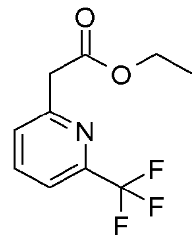
390 mg (51 %) were obtained as a colourless oil.

HPLC-MS (Method 2F): R_t: 11.09 min

MS (ESI pos): m/z = 234 $(M+H)^+$

Example 5S

(6-Trifluoromethyl-pyridin-2-yl)-acetic acid ethyl ester



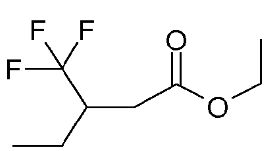
A mixture of caesium carbonate (1.87g, 5.75 mmol) and tri-t-butylphosphine (107 µL, 0.44 mmol) in dry 1,2 dimethoxyethane (10 mL) was treated with tris-(dibenzylideneacetone)di-palladium (81 mg, 0.09 mmol), 2-Bromo-6-(trifluoromethyl)pyridine (1g, 4.42 mmol) and diethylmalonate (0.8 mL, 5.3 mmol) under nitrogen atmosphere. The mixture was heated to 150°C for 30 min in a microwave oven. After cooling to 20°C the mixture was treated with a saturated solution of ammonium chloride (120 mL) and extracted with ethyl ether (3x 80mL). The organic phase was dried and evaporated to give a crude oil that was purified by flash chromatography eluting with n-hexane/ethyl ether 6/1.

460 mg (81 %) were obtained as a colourless oil.

GC (Method 3A): R_t: 8.28 min

MS (EI): m/z = 233 $(M)^+$

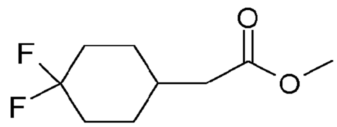
Example 5T, racemic mixture



29 g (148 mmol) of Example 1A was combined with 2 g Pd/C (10 %) and hydrogenated at room temperature (6h, 15 psi). The reaction mixture was filtered and washed with diethyl ether. The solvent was evaporated under reduced pressure (500 mbar, 40°C bath temperature). 27.6 g (94 %) of the product were obtained as a colourless liquid.

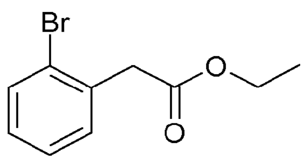
HPLC-MS (Method 1): R_t: 1.65 min

Example 5TA



1.49 g (95 %, 7.43 mmol) was dissolved in 20 ml ethanol and hydrogenated over 150 mg Pd/C (10 %) at atmospheric pressure for 14 h. The mixture was filtered and the solvent removed to yield 1.27 g (89 %) of the product.

Example 5U

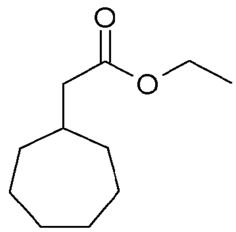
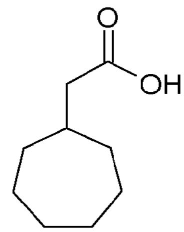
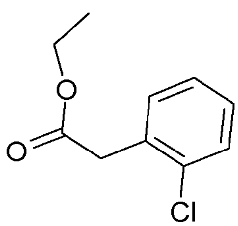
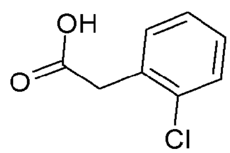
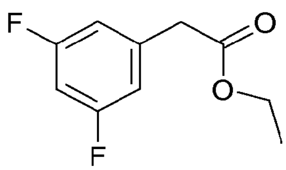
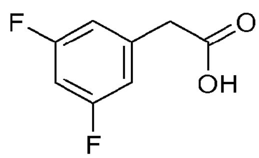
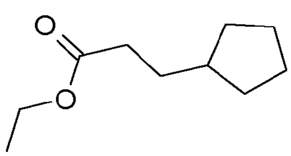
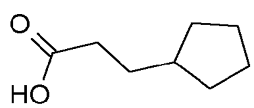
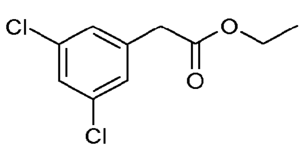
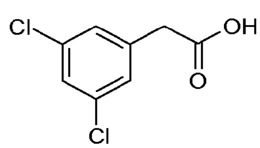
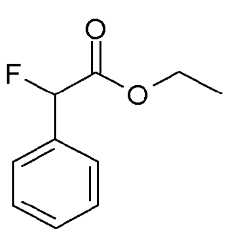
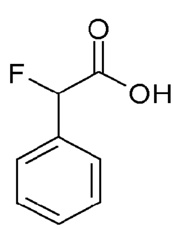


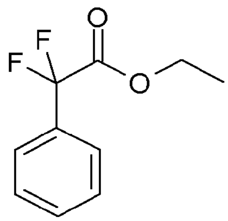
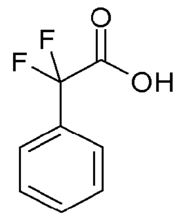
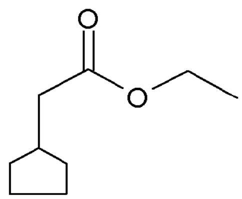
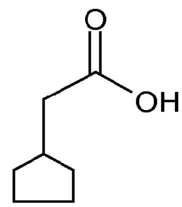
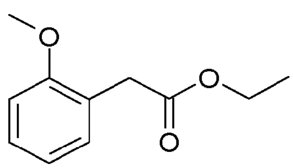
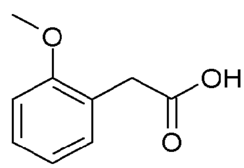
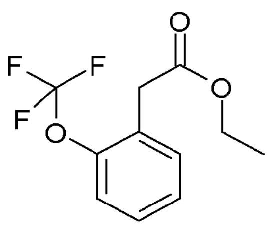
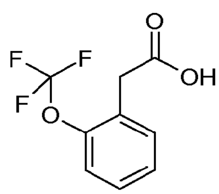
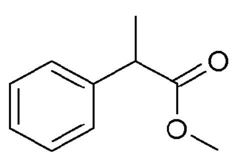
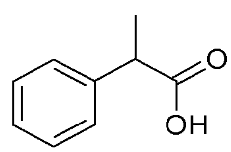
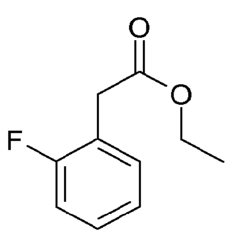
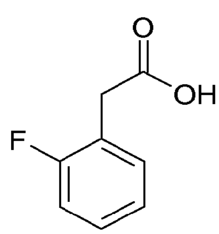
A solution of 15 g (69.8 mmol) of (2-bromo-phenyl)-acetic acid in 50 mL ethanol was cooled to 0°C and 8 mL (110 mmol) thionylchloride was added drop wise. The reaction mixture was heated to 50°C over night. After cooling to room temperature the solvent was removed under reduced pressure. The residue was mixed with ethyl acetate and filtered over 30 g basic aluminium oxide. The filtrate was evaporated under reduced pressure. 18 g (92 %) of the product were obtained.

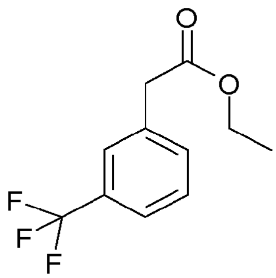
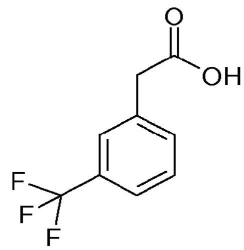
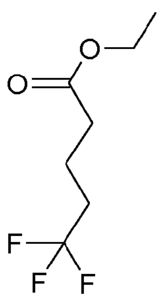
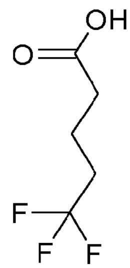
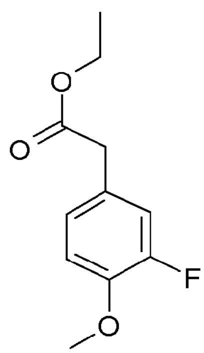
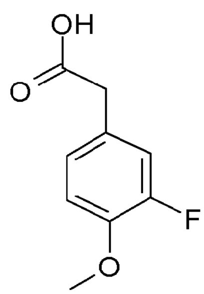
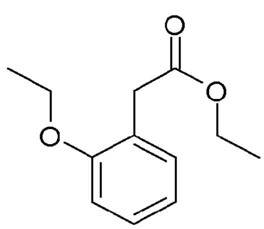
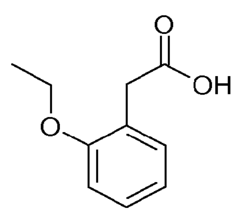
HPLC-MS (Method1): R_t: 1.62 min

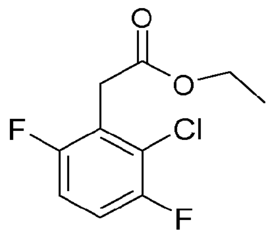
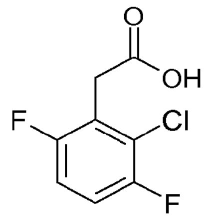
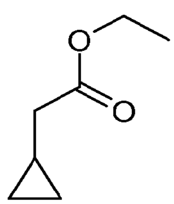
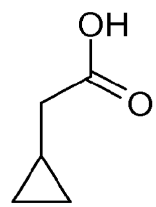
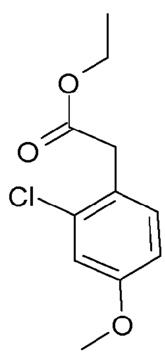
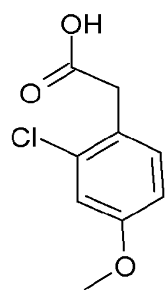
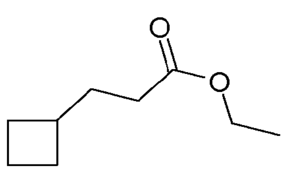
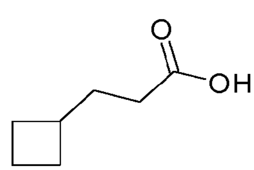
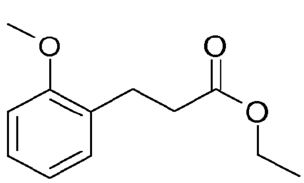
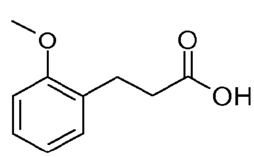
MS (ESI pos): m/z = 243/45 (Br) $(M+H)^+$

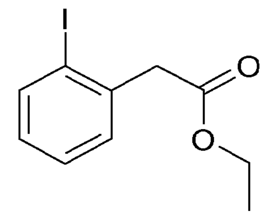
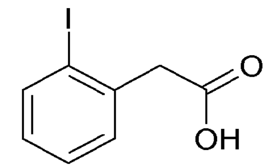
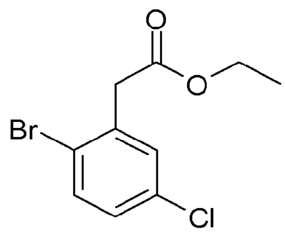
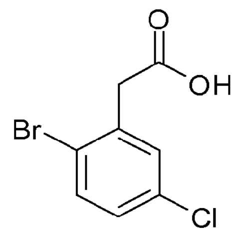
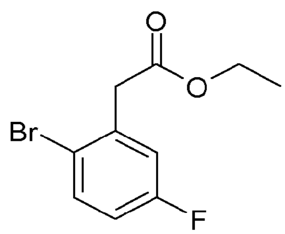
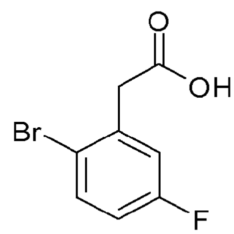
The following examples were synthesized in analogy to the preparation of Example 5U, using the corresponding acids as starting materials.

	structure	starting material	R_t [min]	MS (ESI m/z)
Exp. 5V				185 $(M+H)^+$
Exp. 5Y			1.56 (Method 1)	199/201 (Cl) $(M+H)^+$
Exp. 5W			1.53 (Method 1)	201 $(M+H)^+$
Exp. 5X				171 $(M+H)^+$
Exp. 5Z			1.74 (Method 1)	233/235/237 (2Cl) $(M+H)^+$
Exp. 5AA racem. mixture				133 $(M+H)^+$

Exp. 5AB				201 (M+H)+
Exp. 5AC			1.65 (Method 1)	157/58 (M+H)+
Exp. 5AD			1.36 (Method 1)	195 (M+H)+
Exp. 5AE			1.69 (Method 1)	249/50 (M+H)+
Exp. 5AF racem. mixture				commercially available
Exp. 5AG			1.46 (Method 1)	

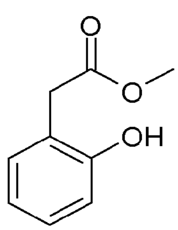
Exp. 5AH			1.63 (Method 1)	
Exp. 5AI				185 $(M+H)^+$
Exp. 5AJ			1.43 (Method 1)	213 $(M+H)^+$
Exp. 5AK				

Exp. 5AL			1.58 (Method 1)	235/237 (Cl) $(M+H)^+$
Exp. 5ALA			1.29 (Method 1)	129 $(M+H)^+$
Exp. 5ALB			1.54 (Method 1)	229/231 (Cl) $(M+H)^+$
Exp. 5ALC			1.62 (Method 1)	157 $(M+H)^+$
Exp. 5ALD			1.56 (Method 1)	209 $(M+H)^+$

Exp. 5ALE			1.59 (Method 1)	291 $(M+H)^+$
Exp. 5ALF			1.86 (Method 5)	277/279/281 $(M+H)^+$ (Cl/Br)
Exp. 5ALG			1.60 (Method 1)	261/263 (Br) $(M+H)^+$

Example 5AM

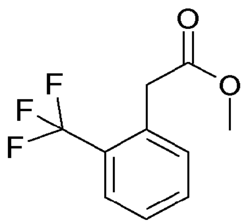
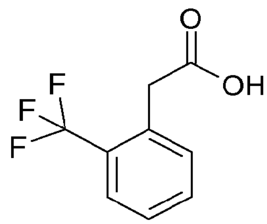
The following example was synthesized in analogy to the preparation of Example 5U, using the corresponding acid as starting material and methanol as solvent.



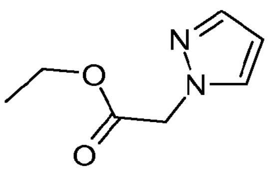
HPLC-MS (Method 1): R_t: 1.04 min

MS (ESI pos): m/z = 167 $(M+H)^+$

The following examples were synthesized in analogy to the preparation of Example 5AM, using the corresponding acids as starting materials.

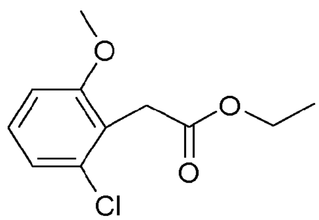
	structure	starting material	R_t [min]	MS (ESI, m/z)
Exp. 5AMA			1.52 (Method 1)	236 $(M+NH_4)^+$

Example 5AN



6.0 g (88.5 mmol) pyrazole was dissolved in 60 mL DMSO and 10.4 g (93 mmol) potassium-tert-butylate was added in portions, keeping the temperature between 20-25°C. The reaction mixture stirred 10 min at room temperature. 10.8 mL (98 mmol) ethyl bromacetate was added drop wise, keeping the temperature between 25-35°C. The reaction mixture was stirred for 2h at room temperature. The reaction mixture was added to a saturated aqueous solution of NaCl and extracted with ethyl acetate. The organic layer was dried, filtered, and the filtrate was evaporated under reduced pressure. The residue was purified by preparative MPLC (SiO_2, eluent dichloromethane / methanol 95/5).10.4 g (38 %) of the product were obtained.

Example 5AO

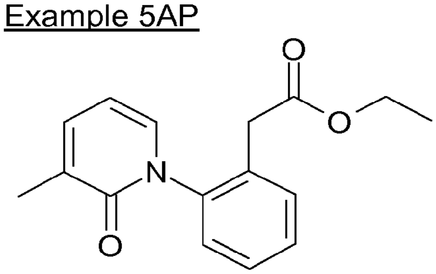


1.83 g (7.7 mmol) of Example 4B was mixed with in 60 mL 4N HCl and cooled with an ice bath. A solution of 1.15 g (16.4 mmol) sodium nitrite in 13.5 mL water was added drop wise. After 10 min a solution of 3.9 g (39.5 mmol) copper(I)chloride in 20 mL conc. HCl was added drop wise. The reaction mixture was allowed to turn to room temperature and stirred for 30 min. The mixture was extracted with ethyl acetate. The organic layer was neutralized with potassium carbonate, filtered over celite and the filtrate extracted with water. The organic layer was dried, filtered and the filtrate was evaporated under reduced pressure. 1.24 g (62 %) of the product were obtained.

HPLC-MS (Method 1): R_t: 1.60 min

MS (ESI pos): m/z = 229/231 (Cl) $(M+H)^+$

<u>Example 5AP</u>



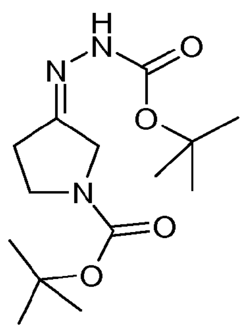
Under argon 1.00 g (4.11 mmol) of example 5U, 540 mg (4.95 mmol) 3-methylpyridone and 80 mg (0.42 mmol) copper-(I) iodide were mixed with 5 ml DMSO and 1.14 g (8.25 mmol) potassium carbonate and 120 mg (0.82 mmol) 8-hydroxyquinoline were added. The mixture was stirred for 48 h at 120°C. After cooling to room temperature the mixture was dissolved in ethyl acetate and washed with 1 M HCl and saturated sodium chloride solution. The organic phase was separated, dried and evaporated. The residue was purified by HPLC (eluent A: water + 0.13 % TFA, eluent B: acetonitrile). The acetonitrile was evaporated and the

remainder extracted with ethyl acetate. The organic phase was dried and evaporated to yield 633 mg (57 %) of the desired product.

HPLC-MS (Method 1): R_t: 1.56 min

MS (ESI pos): m/z = 272 $(M+H)^+$

Example 6A



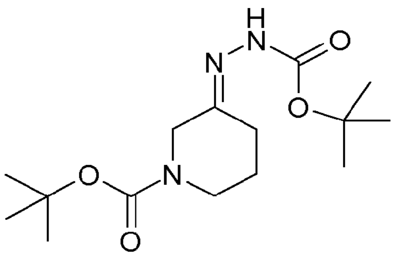
10 g (54 mmol) 1-N-Boc-3-pyrrolidinone was dissolved in 50 mL ethanol and 7.3 g (55.2 mmol) tert-butyl carbazate was added. The reaction mixture was stirred at room temperature for 2h. The solvent was evaporated by reduced pressure. The residue was purified by preparative MPLC (SiO_2, eluent dichloromethane / methanol 95/5). 18 g (89 %) of the product were obtained as oil.

HPLC-MS (Method 1): R_t: 1.35 min

MS (ESI neg.): m/z = 298 $(M-H)^-$

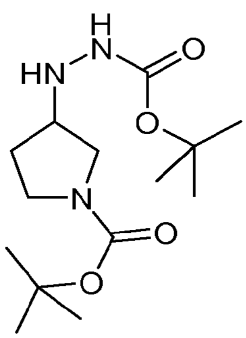
Example 6B

The following example was synthesized in analogy to the preparation of Example 6A, using 1-N-Boc-3-piperidone as starting material.



HPLC-MS (Method 1): R_t: 1.45 min

Example 7A, racemic mixture

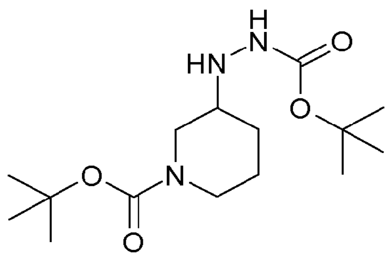


18 g (48 mmol) of Example 6A was dissolved in 300 mL methanol, 2.5 g Pd/C (10 %) was added, and the mixture was hydrogenated at room temperature (8h, 50 psi). The reaction mixture was filtered and the residue washed with methanol. The solvent was evaporated by reduced pressure. 16 g of product were obtained as a colourless oil and used without further purification.

HPLC-MS (Method 1): R_t: 1.36 min

Example 7B, racemic mixture

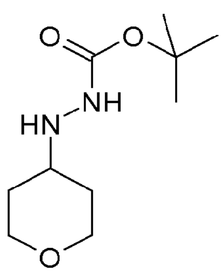
The following example was synthesized in analogy to the preparation of Example 7A, using Example 6B as starting material.



HPLC-MS (Method 1): R_t: 1.42 min

MS (ESI pos): m/z = 316 $(M+H)^+$

Example 7C

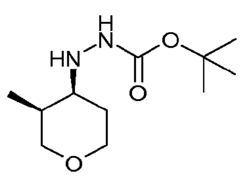
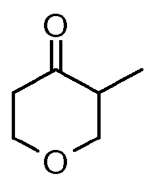
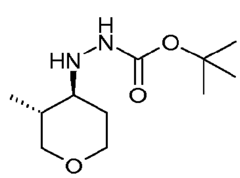
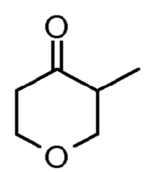
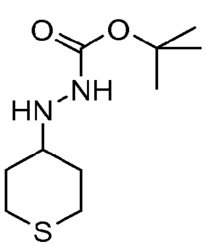
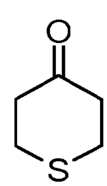


10 g (100 mmol) of tetrahydropyran-4-one was dissolved in 100 mL methanol and 14.5 g (110 mmol) tert-butylcarbazate was added. The reaction mixture was stirred at room temperature for 2h. The solvent was evaporated by reduced pressure. The residue was mixed with 140 mL acetic acid (50 %), 6.9 g (110 mmol) sodium cyanoborohydride was added and the mixture was stirred at room temperature over night. The reaction mixture was neutralized with 4M NaOH and extracted with dichloromethane. The organic layer was washed with a saturated aqueous solution of sodium hydrogen carbonate and a saturated aqueous solution of sodium chloride.

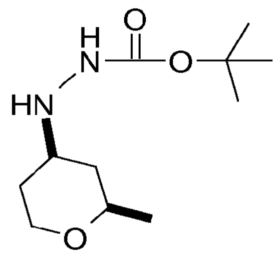
The organic layer was dried over sodium sulphate, filtered, and the filtrate was concentrated under reduced pressure. 19 g (88 %) of the product were obtained as a white solid.

MS (ESI pos): m/z = 217 $(M+H)^+$

The following example was synthesized in analogy to the preparation of Example 7C using the corresponding keton as starting material.

	Structure	starting material: keton	R_t [min]	MS m/z
Example 7CA cis, racem. mixture			11.12 (Method 3A)	174 [EI, $(M-56)^+$]
Example 7CB trans, racem. mixture			11.22 – (Method 3A)	174 [EI, $(M-56)^+$]
Example 7CC			0.99 (Method 1)	177 [ESI, $(M-56+H)^+$]

<u>Example 7D</u>



Cis - racemic mixture

A solution of 2-methyl-tetrahydro-pyran-4-one (2.2 g, 19.7 mmol) in methanol (30 mL) was treated with tert-butyl carbazate (2.6 g, 19.7 mmol) and stirred for 3h at 20°C. Evaporation of solvent affords a white solid that was mixed with 30 mL acetic acid (50 % in water), and treated with sodium cyanoborohydride (1.2 g, 19.7 mmol) portion wise. The mixture was stirred at 20°C for 16h then neutralized with 5N NaOH and extracted with dichloromethane. The organic phase was washed with a saturated solution of $NaHCO_3$ and brine, dried, filtered and evaporated to give a crude solid. Separation of diastereoisomers was obtained by flash chromatography on SiO_2 eluting with a mixture of cyclohexane/ethyl acetate mixture of increasing polarity (from 7/3 to 1/1) to give 1.85 g (41 %) of a white solid.

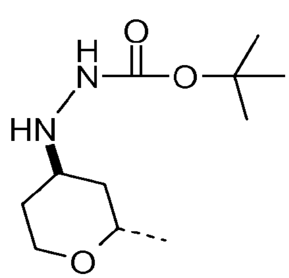
Rf: 0.29 (hexane/ethyl acetate 1:1)

HPLC-MS (Method Grad_90_10_C8_acidic): R_t: 1.79 min

MS (ESI pos): m/z = 131 $(M-100+H)^+$

The cis configuration between methyl and carbazyl group was implied by the ROESY correlation for H-2/H-4.

Example 7E



Trans - Racemic mixture

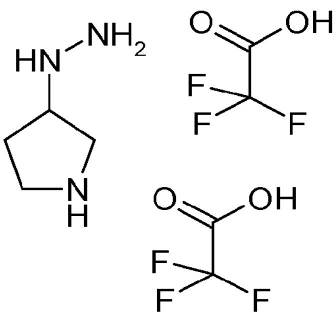
0.7 g (16 %) of a colourless oil were obtained as the second product from flash chromatography of Example 7D

Rf: 0.29 (hexane/ethyl acetate 1:1 stained with Pancaldi's reagent)

HPLC-MS (Method Grad_90_10_C8_acidic): R_t: 1.96 min

MS (ESI pos): m/z = 131 $(M-100+H)^+$

Example 8A, racemic mixture



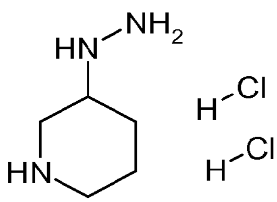
14 g (46.5 mmol) of Example 7A were dissolved in 50 mL dichloromethane, cooled with an ice bath and 25 mL (325 mmol) trifluoroacetic acid was added. The reaction mixture was stirred 3h at room temperature. The solvent was evaporated under reduced pressure. The residue was purified by preparative MPLC (SiO_2, eluent dichloromethane / methanol 8/2). 12 g (78 %) of the product were obtained.

Example 8B

The following example was synthesized in analogy to the preparation of Example 8A, using Example 7C as starting material.

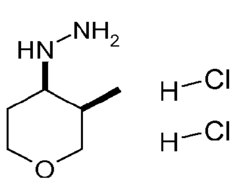
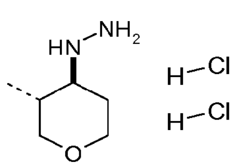
MS (ESI pos): m/z = 117 $(M+H)^+$

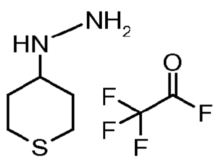
Example 8C, racemic mixture



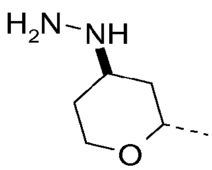
13.0 g (37.1 mmol) of Example 7B were dissolved in 5 mL dioxane and 93 mL (371 mmol) of hydrochloride acid in dioxane (4 M) were added. The reaction mixture was stirred over night at room temperature. 40 mL diethyl ether were added and the mixture stirred 15 min at room temperature. The reaction mixture was filtered. 7.0 g (100 %) of the product were obtained as white solid.

The following examples were synthesized in analogy to the preparation of example 8C using the corresponding Boc-hydrazine as starting material.

	Structure	starting material: Boc-hydrazine	MS m/z
Example 8CA cis, racem. mixture		Example 7CA	131 $(M+H)^+$
Example 8CB trans, racem. mixture		Example 7CB	131 $(M+H)^+$

	Structure	starting material: Boc-hydrazine	MS m/z
Example 8CC		Example 7CC	133 $(M+H)^+$

Example 8D



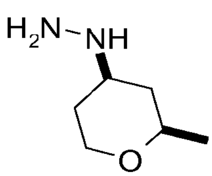
trans - racemic mixture

A solution of Example 7E (700mg, 3 mmol) in dioxane (5 mL) was treated with 4N HCl in dioxane (15 mL, 60 mmol) and the mixture stirred at 20°C for 18h. The solvent was evaporated to give 560 mg (91 %) of a sticky solid that was used in the next step without further purification.

HPLC-MS (Grad_C8_NH_4COOH_Lowmass): R_t: 0.67 min

MS (ESI pos): m/z = 131 $(M+H)^+$

Example 8E



cis -racemic mixture

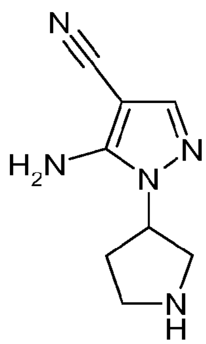
In analogy to the preparation of Example 8D, the title compound was obtained using Example 7D as starting material.

Yield: 68.3 %

HPLC-MS (Method Grad_C8_NH_4COOH_Lowmass): R_t: 0.70 min

MS (ESI pos): m/z = 131 $(M+H)^+$

Example 9A, racemic mixture

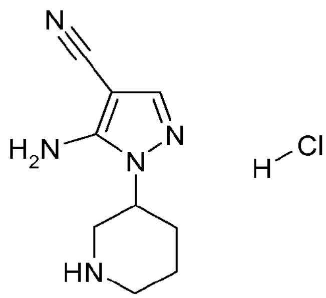
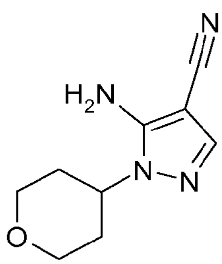
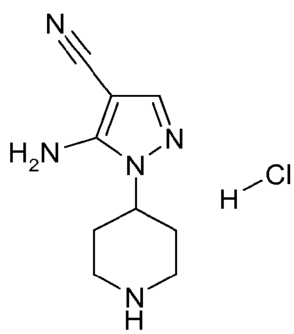
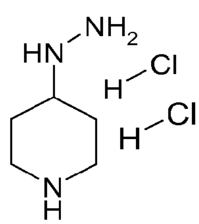
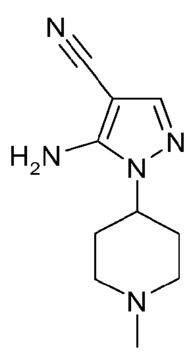
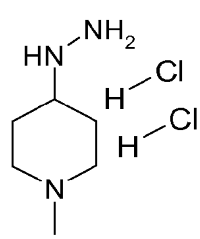


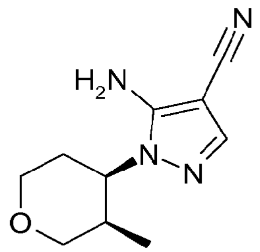
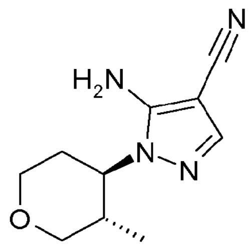
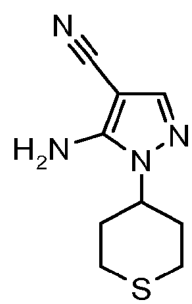
32.0 g (77.8 mmol) of Example 8A was mixed with with 12.0 g (98.3 mmol) of ethoxymethylene-malonodinitrile in 250 mL ethanol, and 40 mL (288 mmol) of triethylamine were added. The reaction mixture was heated to 50°C for 2h. After cooling to room temperature the solvent was removed under reduced pressure. The residue was purified by preparative MPLC (SiO_2, eluent dichloromethane / methanol 8/2).

HPLC-MS (Method 1): R_t: 0.29 min

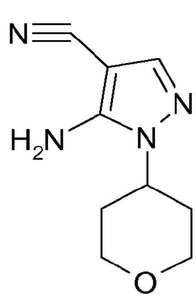
The following examples were synthesized in analogy to the preparation of Example 9A, using the corresponding hydrazines as starting materials.

	structure	starting material	R_t[min]	MS (ESI, m/z)

Exp. 9B racem. mixture		Example 8C	0.59 (Method1)	192 $(M+H)^+$
Exp. 9C		Example 8B	0.76 (Method1)	193 $(M+H)^+$
Exp. 9D			0.32 (Method1)	192 $(M+H)^+$
Exp. 9E			0.40 (Method1)	206 $(M+H)^+$

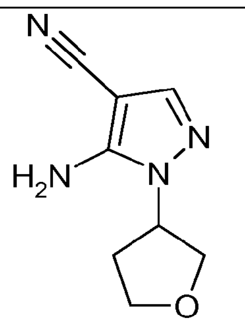
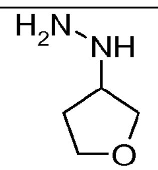
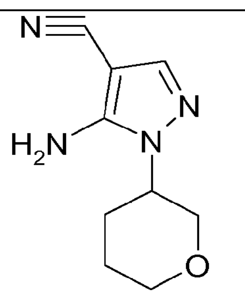
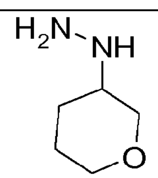
Example 9EA cis, racem. mixture		Example 8CA	1.90 Grad C8-NH_4CCOH	207 $(M+H)^+$
Example 9EB trans, racem. mixture		Example 8CB	1.87 Grad C8-NH_4CCOH	207 $(M+H)^+$
Example 9EC		Example 8CC	1.01 (Method1)	209 $(M+H)^+$

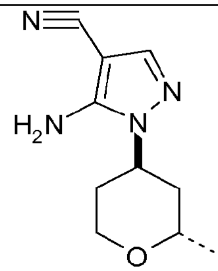
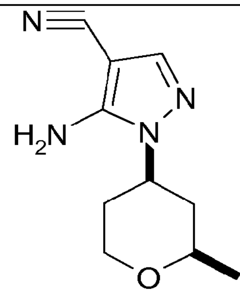
Example 9F



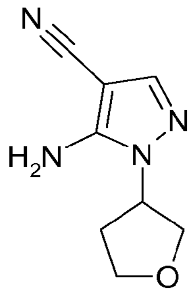
A mixture of 4.4 g (38 mmol) of (tetrahydro-pyran-4-yl)-hydrazine and 4.7 g (38 mmol) of ethoxymethylene-malononitrile in 90 mL of ethanol and 10.5 mL (103 mmol) of triethylamine was stirred at 50°C for 30 min. After cooling to 20°C the solvent was removed under reduced pressure and the residue was treated with a mixture of water / dichloromethane = 1/1. The resulting suspension was stirred for 15 min and then filtered to give a yellow solid that was washed subsequently with dichloromethane, water and dichloromethane. The solid was dried at 45°C under reduced pressure. 2.7 g (37 %) of the title compound were obtained as yellow solid and used in the next step without further purification.

The following examples were synthesized in analogy to the preparation of Example 9F, using the corresponding hydrazines as starting materials:

	Structure	starting material: hydrazine	R_t [min]	MS m/z
Example 9G racem. mixture			1.31 (Method Grad_90_10_C8_acidic)	179 $(M+H)^+$
Example 9H racem. mixture			4.97 (Method 1E hydro)	193 $(M+H)^+$

	Structure	starting material: hydrazine	R_t [min]	MS m/z
Example 9I trans; racem. mixture		Example 8D	2.14 (Method Grad_10_90_C8_acidic)	207 $(M+H)^+$
Example 9J cis; racem. mixture		Example 8E	1.91 (Method Grad_10_90_C8_acidic)	207 $(M+H)^+$

Example 9GA (Enantiomer A)



Enantiomer A

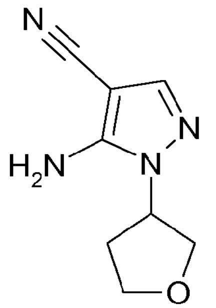
Example 9G was submitted for chiral separation to isolate its enantiomers. The enantiomer labeled A, of unknown but single stereochemistry was isolated using the following conditions.

Amount supplied	5g
Chiral Column	Daicel Chiralpak AD 50 x 300 mm
Mobile phase	n-Hexane (60%)/methyl-tert-butyl ether (40%) /Ethanol (5 %) v/v
Flow rate	20 mL/min
Detection	UV at 254 nm
Injection mode	continuous

Obtained 1g of enantiomer A.

Enantiomeric excess 99.3%; retention time 27.83 min; (analytical method: Chiral 3)

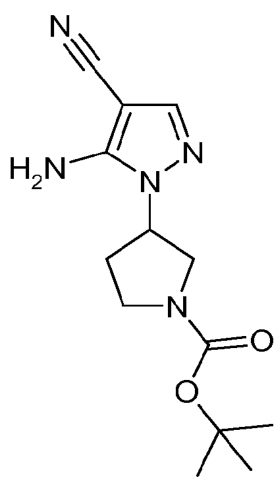
Example 9GB (Enantiomer B)



Enantiomer B

Isolated using the same conditions as enantiomer A, obtaining 0.5 g ; enantiomeric excess 96.7%; R_t:30.94 min; (analytical method: Chiral 3).

Example 10A, racemic mixture

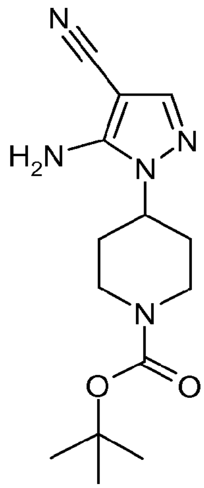
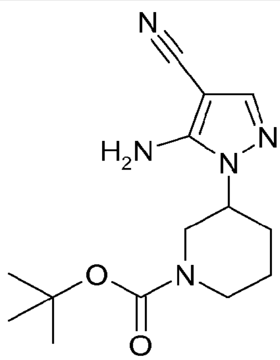


4.0 g (22.6 mmol) of Example 9A were mixed with in 60 mL tetrahydrofuran, and 5.7 g (30 mmol) di-tert-butyl-dicarbamate was added. The reaction mixture was heated to 60°C for 5h. After cooling to room temperature the solvent was removed under reduced pressure. The residue was purified by preparative MPLC (SiO_2, eluent dichloromethane/methanol 9/1).

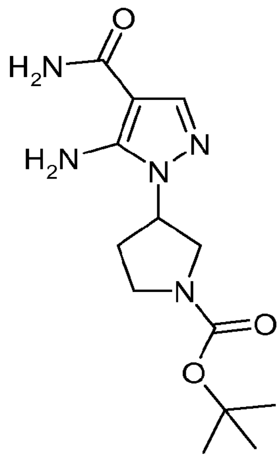
HPLC-MS (Method 1): R_t: 1.28 min

MS (ESI pos): m/z = 278 $(M+H)^+$

The following examples were synthesized in analogy to the preparation of Example 10A, using the corresponding pyrazoles as starting materials.

	structure	starting material	R_t [min]	MS (ESI, m/z)
Exp. 10B		Example 9D	1.30 (Method 1)	292 $(M+H)^+$
Exp. 10C racem. mixture		Example 9B	1.33 (Method 1)	292 $(M+H)^+$

Example 11A, racemic mixture



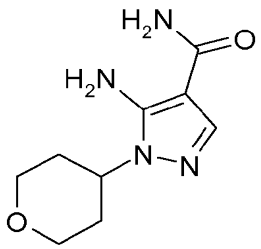
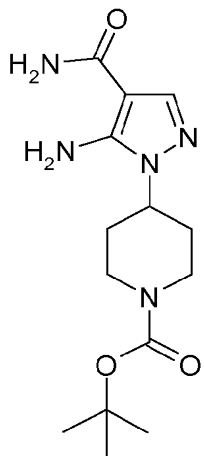
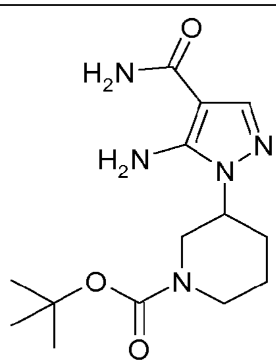
2.4 g (8.96 mmol) of Example 10A were dissolved in 30 mL ethanol. At room temperature a solution of 10 mL (120 mmol) hydrogen peroxide (35 % in water) and 50 mL ammonia (25 % in water) was added slowly over a period of 10 min. The reaction mixture was stirred at room temperature for 2h. The solution was carefully concentrated to a volume of 50 mL under reduced pressure. A precipitate formed and was collected by filtration. 1.3 g (50 %) of the product were obtained as a solid.

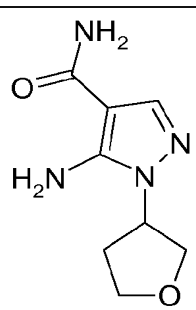
HPLC-MS (Method 1): R_t: 1.08 min

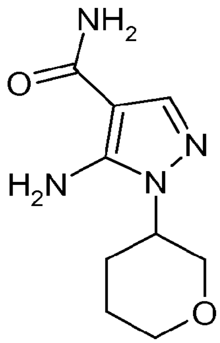
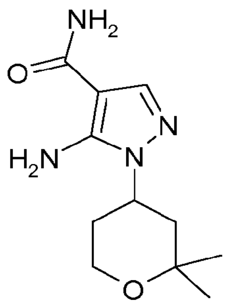
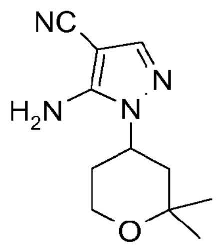
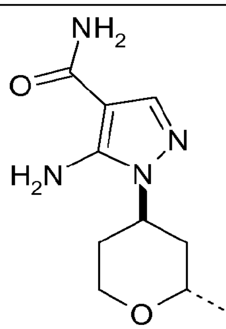
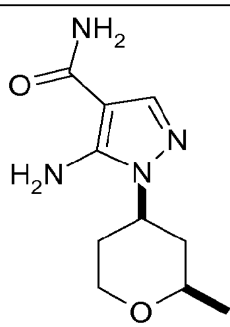
MS (ESI pos): m/z = 296 $(M+H)^+$

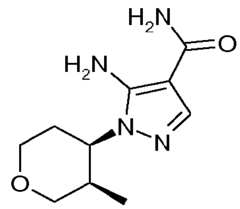
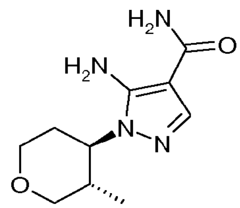
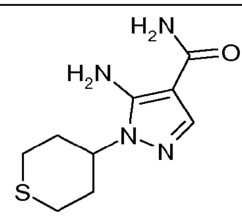
The following examples were synthesized in analogy to the preparation of Example 11A, using the corresponding pyrazoles as starting materials.

	structure	starting material	R_t [min]	MS (ESI pos/neg, m/z)

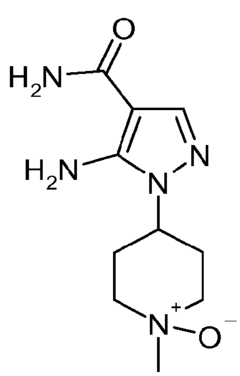
Exp. 11B		Example 9C	0.44 (Method 1)	211 $(M+H)^+$
Exp. 11C		Example 10B	1.12 (Method 1)	308 $(M-H)^-$
Exp. 11D racem. mixture		Example 10C	1.13 (Method 1)	310/311 $(M+H)^+$ HPLC-MS

Exp. 11E racem. mixture		Example 9G	2.39 (Method 2F)	197 $(M+H)^+$

Exp. 11F racem. mixture		Example 9H	0.95 (Method Grad_C8_NH$_4$COOH)	211 $(M+H)^+$
Exp. 11G racem. mixture			1.57 (Method Grad_C8_NH$_4$COOH)	339 $(M+H)^+$
Exp. 11H trans, racem. mixture		Example 9I	1.27 (Method Grad_90_10_C8_acidic)	225 $(M+H)^+$
Exp. 11I cis, racem. mixture		Example 9J	1.27 (Method Grad_90_10_C8_acidic)	225 $(M+H)^+$

Example 11IA cis, racem. mixture		Example 9EA	1.11 (Method Grad_C8_NH 4COOH)	225 $(M+H)^+$
Example 11IB trans, racem. mixture		Example 9EB	1.14 (Method Grad_C8_NH 4COOH)	225 $(M+H)^+$
Example 11IC		Example 9EC		227 $(M+H)^+$

Example 11J, racemic mixture

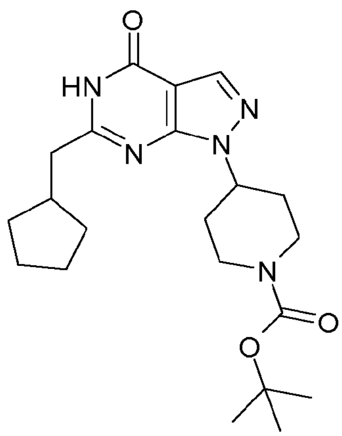


2.30 g (11.2 mmol) of Example 9E were dissolved in 6 mL dimethylsulfoxide. Under ice cooling 8 mL (77.6 mmol) hydrogen peroxide and 1.7 g (12.3 mmol) potassium carbonate were added. Then the reaction mixture was stirred 15 min at room temperature. The reaction mixture was cooled with an ice bath, 100 mL of water were

added and extracted with dichloromethane. The water phase was evaporated under reduced pressure. The residue was mixed with in dichloromethane and filtered. 2.8 g (52 %) of the product were obtained as a white solid.

HPLC-MS (Method1): R_t: 0.24 min

Example 12A

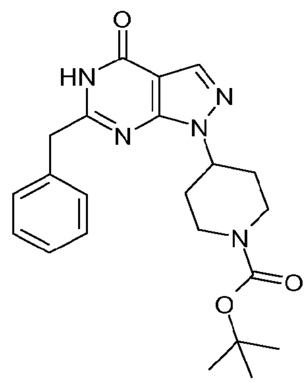
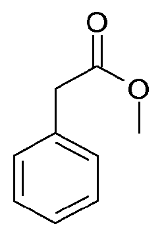
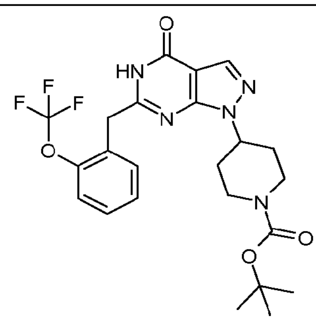
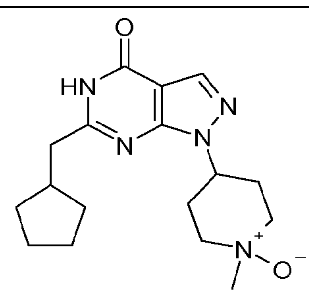


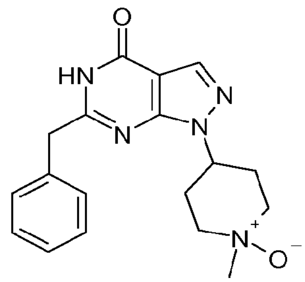
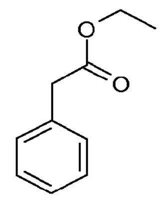
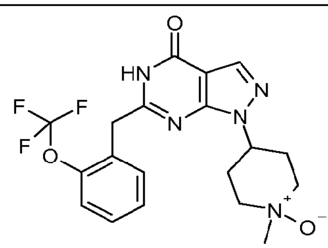
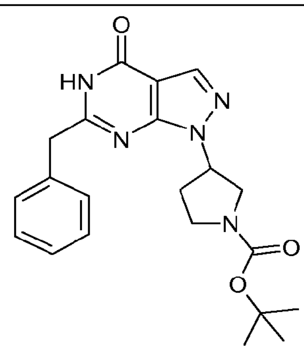
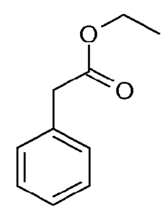
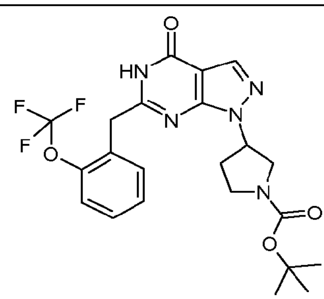
660 mg (2.13 mmol) of Example 11C were dissolved in 15 mL of absolute ethanol. 1.85 g (10.7 mmol) of Example 5AC and 430 mg (10.7 mmol) of sodium hydride (60 % suspension in mineral oil) were added. The reaction mixture was heated to 150°C for 30 min in a microwave oven. Cooling to room temperature was followed by evaporation of the solvent under reduced pressure. The residue was purified by preparative HPLC (eluent A: water + 0.13 % TFA, eluent B: acetonitrile). 320 mg (38 %) of the product were obtained as a white solid.

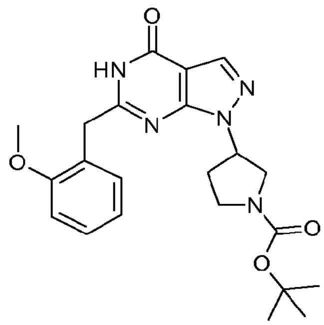
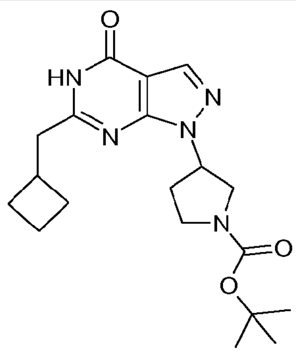
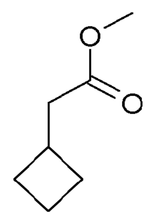
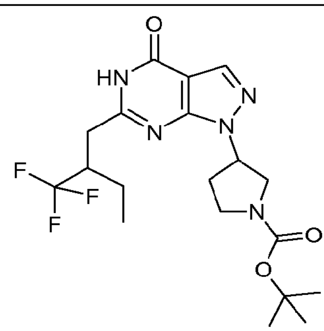
HPLC-MS (Method1): R_t: 1.61 min

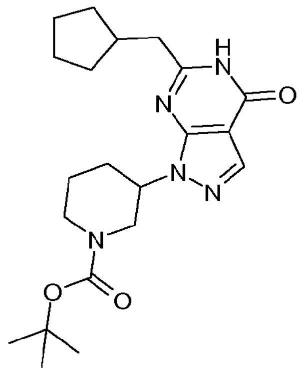
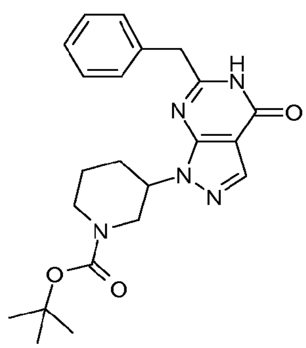
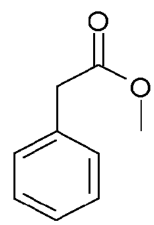
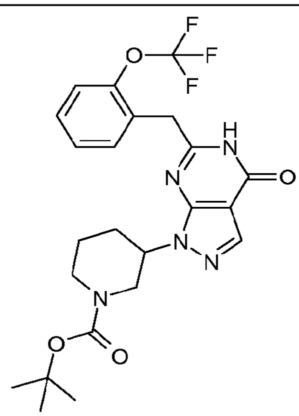
MS (ESI pos): m/z = 402 $(M+H)^+$

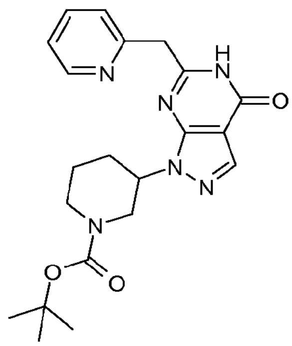
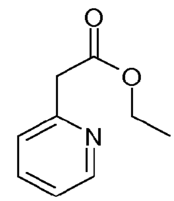
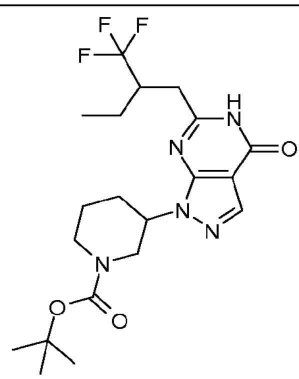
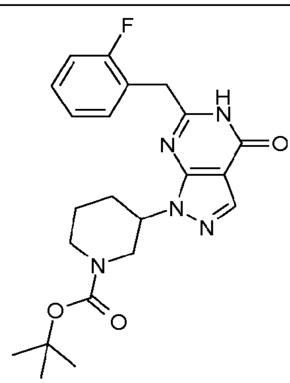
The following examples were synthesized in analogy to the preparation of Example 12A, using the corresponding pyrazoles and esters as starting materials.

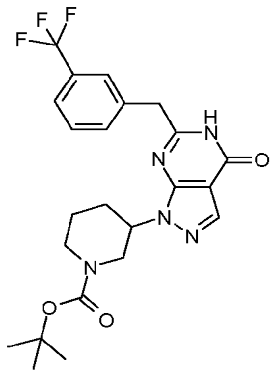
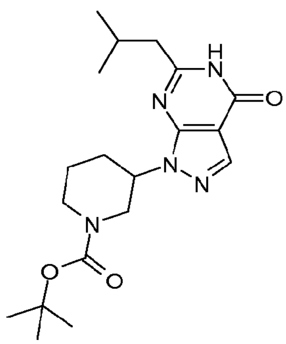
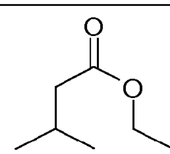
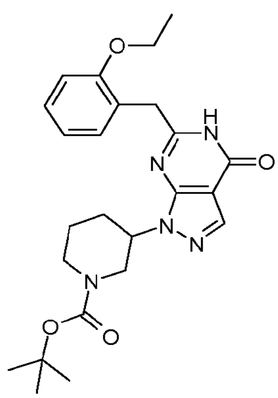
	Structure	starting material: pyrazole	starting material: ester	R_t [min]	MS (ESI pos/neg, m/z)
Exp. 12B		Exp. 11C		1.52 (Method 1)	410 $(M+H)^+$
Exp. 12C		Exp. 11C	Example 5AE	1.66 (Method 1)	492 $(M-H)^-$
Exp. 12D mixture of stereoisomers		Exp. 11J	Example 5AC	1.02 (Method 1)	332 $(M+H)^+$

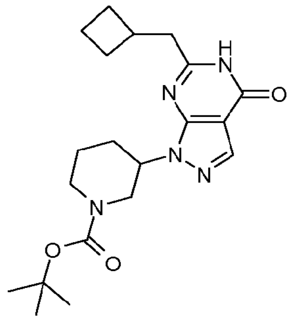
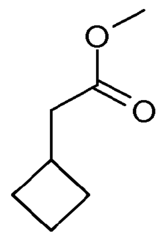
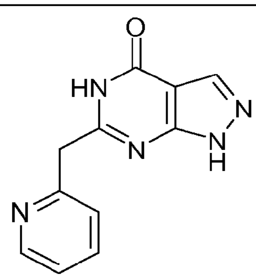
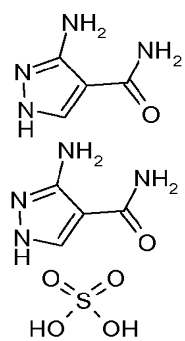
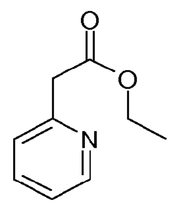
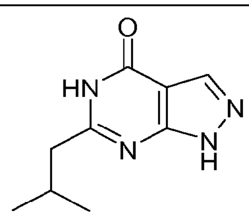
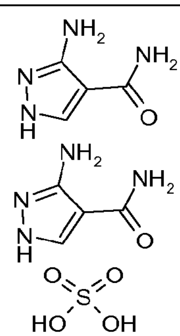
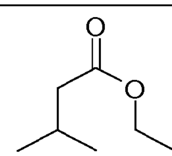
	Structure	starting material: pyrazole	starting material: ester	R_t [min]	MS (ESI pos/neg, m/z)
Exp. 12E mixture of stereoisomers		Exp. 11J		0.96 (Method 1)	340 $(M+H)^+$
Exp. 12F mixture of stereoisomers		Exp. 11J	Example 5AE	1.12 (Method 1)	424 $(M+H)^+$
Exp. 12G racem. mixture		Exp. 11A		1.49 (Method 1)	396 $(M+H)^+$
Exp. 12H racem. mixture		Exp. 11A	Example 5AE	1.62 (Method 1)	480 $(M+H)^+$

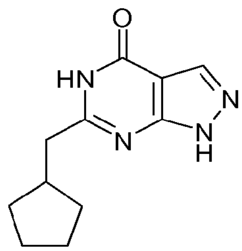
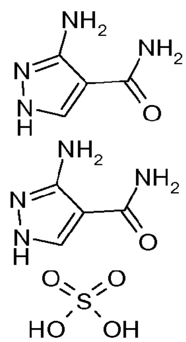
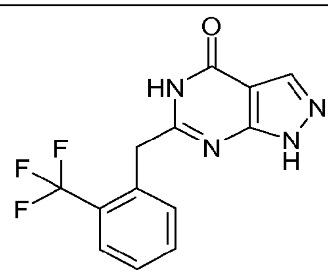
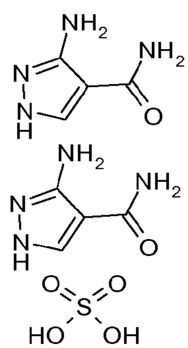
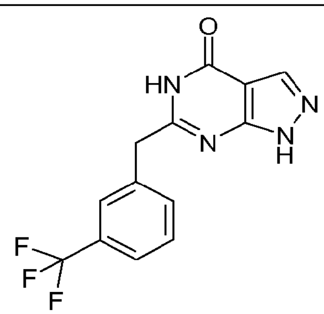
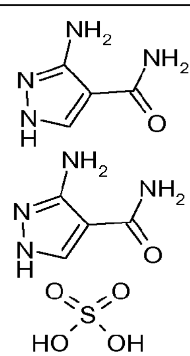
	Structure	starting material: pyrazole	starting material: ester	R_t [min]	MS (ESI pos/neg, m/z)
Exp. 12I racem. mixture		Exp. 11A	Example 5AD	1.52 (Method 1)	426 $(M+H)^+$
Exp. 12J racem. mixture		Exp. 11A		1.49 (Method 1)	374 $(M+H)^+$
Exp. 12K mixture of stereoisomers		Exp. 11A	Example 5T	1.58 (Method 1)	428 $(M-H)^-$

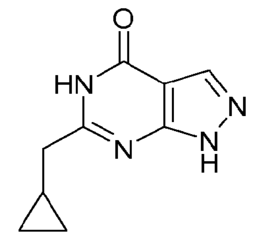
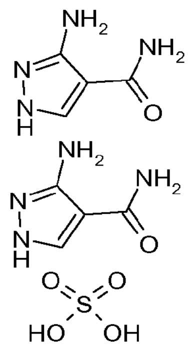
	Structure	starting material: pyrazole	starting material: ester	R_t [min]	MS (ESI pos/neg, m/z)
Exp. 12L racem. mixture		Exp. 11D	Example 5AC	1.65 (Method 1)	402 $(M+H)^+$
Exp. 12M racem. mixture		Exp. 11D		1.55 (Method 1)	408 $(M+H)^+$
Exp. 12N racem. mixture		Exp. 11D	Example 5AE	1.67 (Method 1)	494 $(M+H)^+$

	Structure	starting material: pyrazole	starting material: ester	R_t [min]	MS (ESI pos/neg , m/z)
Example 12O racem. mixture		Exp. 11D		1.13 (Method 1)	411 $(M+H)^+$
Exp. 12P mixture of stereoisomers		Exp. 11D	Example 5T	1.63 (Method 1)	444 $(M+H)^+$
Exp. 12Q racem. mixture		Exp. 11D	Example 5AG	1.53 (Method 1)	428 $(M+H)^+$

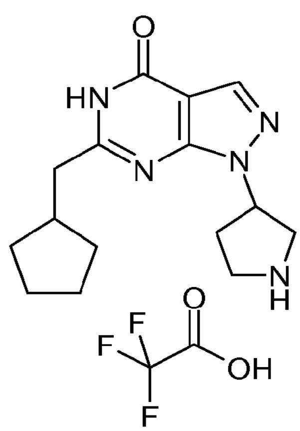
	Structure	starting material: pyrazole	starting material: ester	R_t [min]	MS (ESI pos/neg , m/z)
Exp. 12R racem. mixture		Exp. 11D	Example 5AH	1.66 (Method 1)	478 $(M+H)^+$
Exp. 12S racem. mixture		Exp. 11D		1.51 (Method 1)	376 $(M+H)^+$
Exp. 12T racem. mixture		Exp. 11D	Example 5AK	1.63 (Method 1)	454 $(M+H)^+$

	Structure	starting material: pyrazole	starting material: ester	R_t [min]	MS (ESI pos/neg, m/z)
Exp. 12U racem. mixture		Exp. 11D		1.56 (Method 1)	388 $(M+H)^+$
Exp. 12V				1.77 (Method 2F)	228 $(M+H)^+$
Exp. 12W				6.96 (Method 2F)	193 $(M+H)^+$

	Structure	starting material: pyrazole	starting material: ester	R_t [min]	MS (ESI pos/neg, m/z)
Exp. 12X			Example 5AC	8.28 (Method 2F)	219 $(M+H)^+$
Exp. 12Y			Example 5AMA	9.15 (Method 2F)	295 $(M+H)^+$
Example 12Z			Example 5AH	9.54 (Method 2F)	295 $(M+H)^+$

	Structure	starting material: pyrazole	starting material: ester	R_t [min]	MS (ESI pos/neg, m/z)
Example 12AA			Example 5ALA	6.48 (Method 2F)	191 $(M+H)^+$

Example 13A, racemic mixture



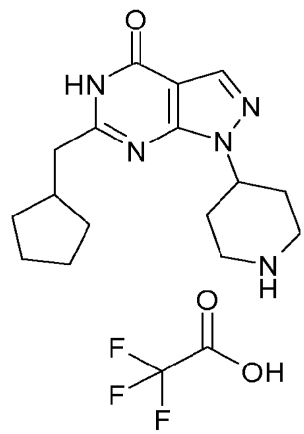
400 mg (1.35 mmol) of Example 11A were dissolved in 8 mL of absolute ethanol, 840 mg (5.4 mmol) of Example 5AC and 220 mg (5.5 mmol) of sodium hydride (60 % suspension in mineral oil) were added. The reaction mixture was heated to 150°C for 30 min in a microwave oven. After cooling to room temperature the reaction mixture was acidified with 4N hydrochloride acid. The solvent was removed under reduced pressure. The residue was purified by preparative HPLC (eluent A: water + 0.13 %

TFA, eluent B: acetonitrile). 250 mg (46 %) of the product were obtained as a white solid.

HPLC-MS (Method 1): R_t: 0.93 min

MS (ESI pos): m/z = 288 $(M+H)^+$

Example 13B



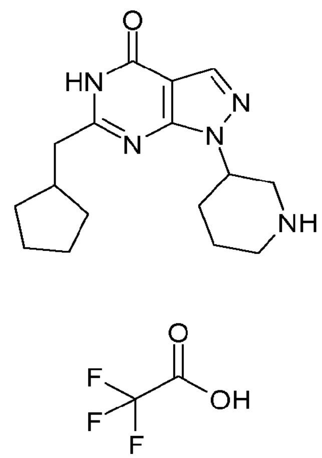
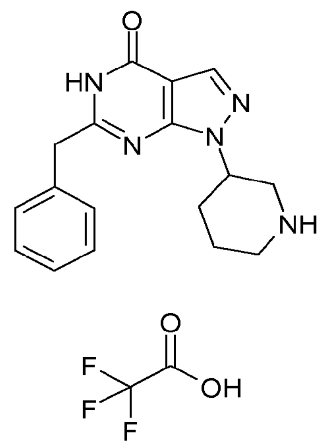
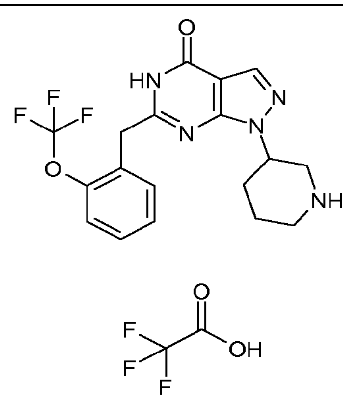
330 mg (0.82 mmol) of Example 12A was dissolved in 3 mL dichloromethane and 1 mL trifluoroacetic acid was added. The reaction mixture was stirred at room temperature over night. The solvent was evaporated under reduced pressure. The remaining product was purified by preparative HPLC (eluent A: water + 0.13 % TFA, eluent B: acetonitrile). 240 mg (70 %) of the product were obtained.

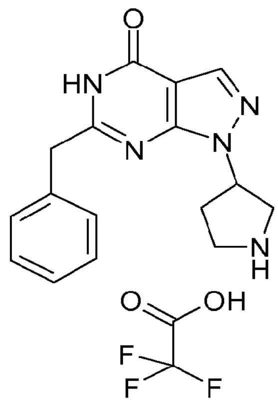
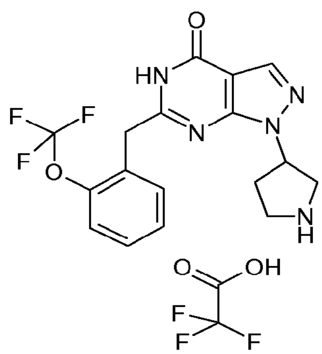
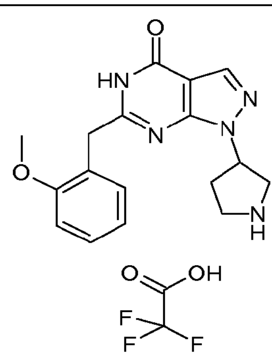
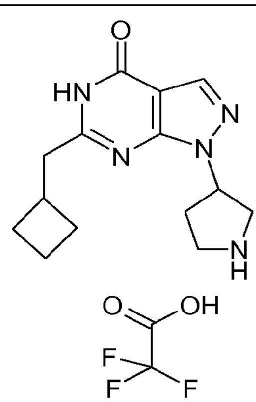
HPLC-MS (Method 1): R_t: 0.96 min

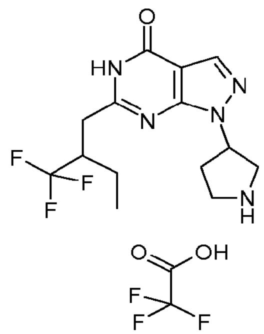
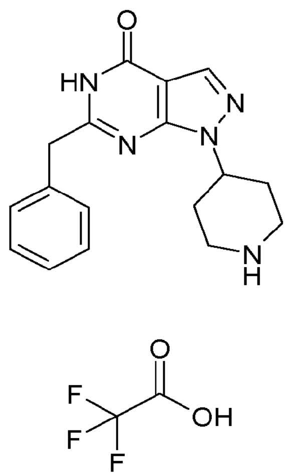
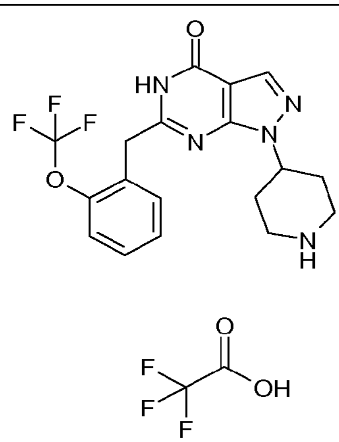
MS (ESI pos): m/z = 302 $(M+H)^+$

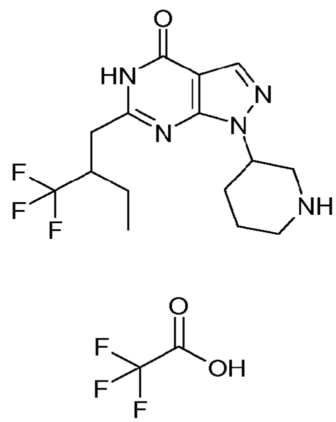
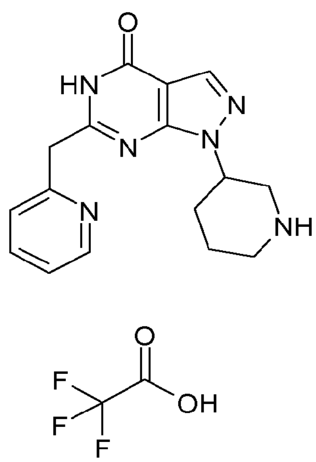
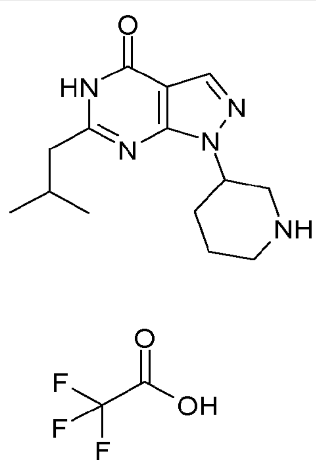
The following examples were synthesized in analogy to the preparation of Example 13B, using the corresponding Boc-protected amines as starting materials

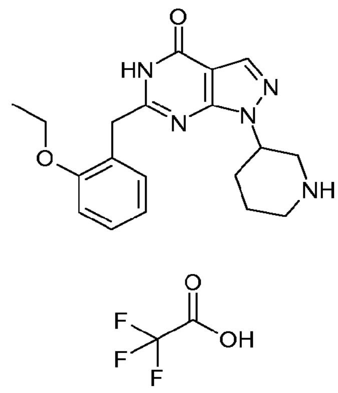
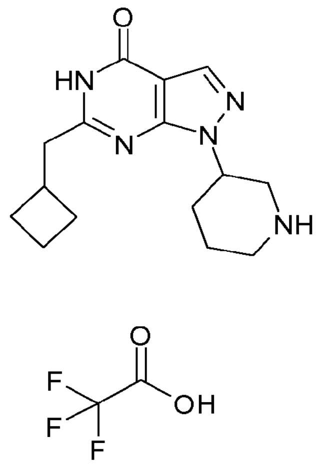
	Structure	starting material	R_t [min]	MS (ESI, m/z)

Exp. 13C racem. mixture		Exp. 12L	1.01 (Method 1)	302 $(M+H)^+$
Exp. 13D racem. mixture		Exp. 12M	0.93 (Method 1)	310 $(M+H)^+$
Exp. 13E racem. mixture		Exp. 12N	1.09 (Method 1)	394 $(M+H)^+$

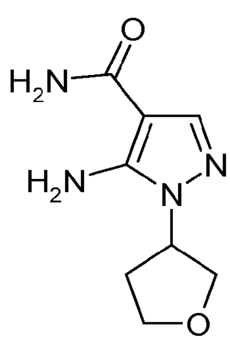
Exp. 13F racem. mixture		Exp. 12G	0.92 (Method 1)	296 $(M+H)^+$
Exp. 13G racem. mixture		Exp. 12H	1.08 (Method 1)	380 $(M+H)^+$
Exp. 13H racem. mixture		Exp. 12I	0.96 (Method 1)	326 $(M+H)^+$
Exp. 13I racem. mixture		Exp. 12J	0.89 (Method 1)	274 $(M+H)^+$

Exp. 13J racem. mixture		Exp. 12K	1.0 (Method1)	330 $(M+H)^+$
Exp. 13K		Exp. 12B	0.92 (Method1)	310 $(M+H)^+$
Exp. 13L		Exp. 12C	1.07 (Method1)	394 $(M+H)^+$

Exp. 13M mixture of stereoisomers		Exp. 12P	1.04 (Method 1)	344 $(M+H)^+$
Exp. 13N racem. mixture		Exp. 12O	0.37 (Method 1)	319 $(M+H)^+$
Exp. 13O racem. mixture		Exp. 12S	0.89 (Method 1)	276 $(M+H)^+$

Exp. 13P racem. mixture		Exp. 12T	1.04 (Method 1)	354 $(M+H)^+$
Exp. 13Q racem. mixture		Exp. 12U	0.94 (Method 1)	288 $(M+H)^+$

Example 15A:



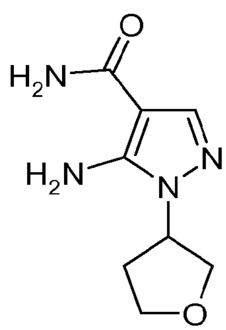
Enantiomer A

200 mg (1.12 mmol) of Example 9GA was mixed with 4.5 mL ammonia solution (30 % in water). The reaction mixture was heated to 130°C for 30 min in a microwave oven. Cooling to room temperature was followed by evaporation of the solvent under reduced pressure. 180 mg (82 %) of the product were obtained.

GC-MS (Method 3A. 1): R_t: 12.62 min

$[M]^+$ = 196

Example 16A:



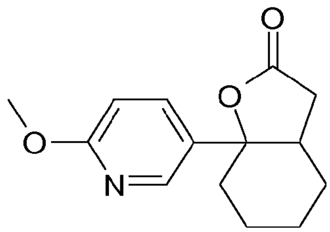
Enantiomer B

150 mg (0.84 mmol) of Example 9GB were mixed with 2.10 mL ammonia solution (30 % in water). The reaction mixture was heated to 130°C for 30 min in a microwave oven. Cooling to room temperature was followed by evaporation of the solvent under reduced pressure. 100 mg (60 %) of the product were obtained.

GC-MS (Method 3A. 2): R_t: 12.59 min

$[M]^+$ = 196

Example 17A, mixture of stereoisomers

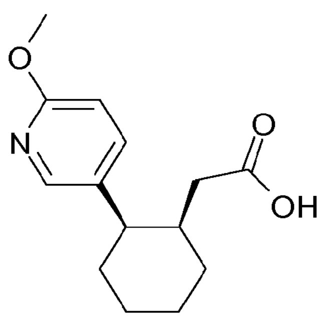


A solution of 1.00 g (5.32 mmol) 2-methoxy-5-bromopyridine in 10 mL anhydrous THF was cooled to -78°C and n-BuLi (3.66 mL, 5.85 mmol, 1.6 M in hexane) was added. After 10 min at -78°C 1.18 g (6.38 mmol) 2-oxo-cyclohexyl-acetic acid ethyl ester was added and the mixture was warmed to 25 °C. Water was added (1 mL) and the mixture was concentrated under reduced pressure. The residue was purified by preparative HPLC (eluent A: water + 0.13 % TFA, eluent B: acetonitrile). 370 mg (28 %) of the product were obtained as an oil.

HPLC-MS (Method 1): R_t: 1.23 min

MS (ESI pos): m/z = 248 $(M+H)^+$

Example 18A, cis, racemic mixture

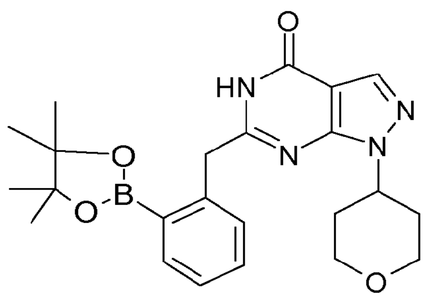


380 mg (1.54 mmol) of Example 17A was mixed with 5 mL methanol, 50 mg Pd/C (10 %) was added, and the mixture was hydrogenated at room temperature (8h, 50 psi). The reaction mixture was filtered and the residue was washed with methanol. The solvent was evaporated under reduced pressure. 340 mg (89 %) of product were obtained as colourless oil and used without further purification.

HPLC-MS (Method 1): R_t: 1.01 min

MS (ESI pos): m/z = 250 $(M+H)^+$

Example19A



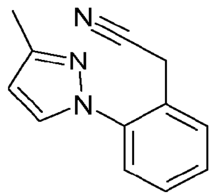
100 mg (0.48 mmol) of Example 11B were dissolved in 2 mL of absolute ethanol, 346 mg (1.43 mmol) of [2-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-acetonitrile and 25.3 mg (0.63 mmol) of sodium hydride (60 % suspension in mineral oil) were added. The reaction mixture was heated to 130°C for 40 min in a microwave oven; cooling to room temperature was followed by addition of 25.3 mg (0.63 mmol) of sodium hydride (60 % suspension in mineral oil) and a second microwave irradiation (130 °C; 40 min). Cooling to room temperature was followed by addition of ammonium chloride and dichloromethane; the two phases were sepated and the residue was purified by flash chromatography on SiO2. 55 mg (26 %) of the product were obtained as a solid.

HPLC-MS (Method 1E hydro): R_t: 9.98 min

MS (APCI pos): m/z = 331 $(M+H)^+$

<u>Example 20A</u>

[2-(3-Methyl-pyrazol-1-yl)-phenyl]-acetonitrile



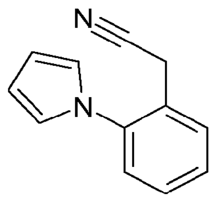
A round bottom flask was charged under inert atmosphere with copper iodide (760 mg, 4 mmol), cesium carbonate (3.91 g, 12 mmol) then dimethylformamide (20 mL), previously degassed, was added followed by 2-Bromophenylacetonitrile (519 µL, 4 mmol), 3-Methylpyrazole (3.32 mL, 40 mmol) and N-N'-dimethylethylenediamine (425.86 µL, 4 mmol). The reaction mixture was heated to 120 °C for 2.5 hours. After cooling the reaction mixture was filtered through a Celite pad that was rinsed with dimethylformamide. The volume was reduced under reduced pressure, saturated ammonium chloride aqueous solution was added and extracted with ethyl acetate. The organic phase was washed with saturated aqueous NH_4Cl solution, brine then dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on SiO_2 using cyclohexane/ethyl acetate mixture of increasing polarity (from 100% cyclohexane to 100% ethyl acetate) as eluent. The oil obtained was further purified by SPE Stratosphere "PL-THIOL MP" to completely remove copper salts. The title compound was obtained as a thick dark oil (300 mg, 38 %).

GC-MS (Method 3A.1): R_t: 10.47 min

MS: 197 $[M]^{+\cdot}$

Example 21A

(2-Pyrrol-1-yl-phenyl)-acetonitrile



Under inert atmosphere a solution of 500 mg (3.783 mmol) of 2-Aminophenylacetonitrile and 1 mL (7.566 mmol) of 2,5-Dimethoxytetrahydrofuran in 5 mL of acetic acid was heated to 60 °C for 2 hours. After cooling the reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography on SiO_2 using cyclohexane/ethyl acetate mixture of increasing polarity (from 100% cyclohexane to 100% ethyl acetate) as eluent. The title compound was obtained as a light yellow oil (470 mg, 68.2%).

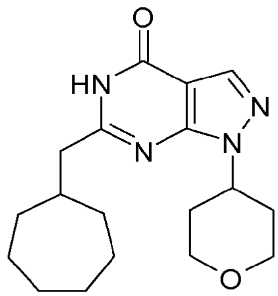
GC-MS (Method 3A): R_t: 9.75 min

MS: 182 $[M]^{+\cdot}$

<u>Exemplary embodiments:</u>

The following section presents for illustration compounds that have PDE 9 inhibiting properties, be it for to illustrate the compounds according to the invention or to provide insight in their manufacturing process. Among these examples are the compounds that are subject to the present invention. Further details about the scope of the present invention are given in the description.

Example1



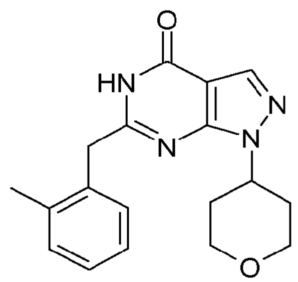
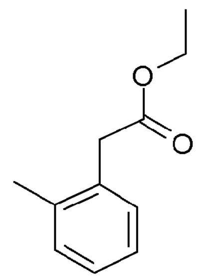
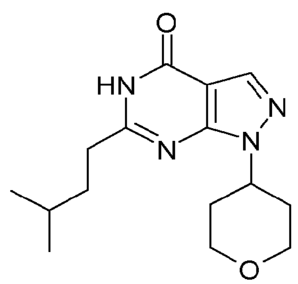
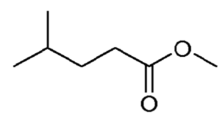
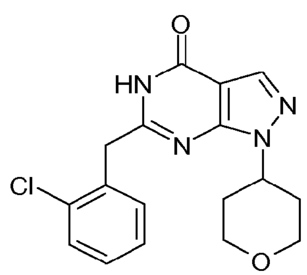
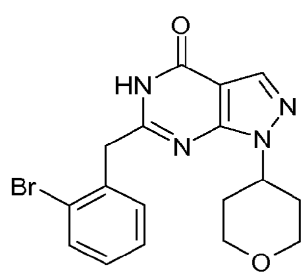
100 mg (0.48 mmol) of Example 11B were dissolved in 5 mL of absolute ethanol, 400 mg (2.17 mmol) of Example 5V and 100 mg (2.5 mmol) of sodium hydride (60 % suspension in mineral oil) were added. The reaction mixture was heated to 150°C for 30 min in a microwave oven. Cooling to room temperature was followed by evaporation of the solvent under reduced pressure. The residue was purified by preparative HPLC (eluent A: water + 0.13 % TFA, eluent B: acetonitrile). 29 mg (18 %) of the product were obtained as a white solid.

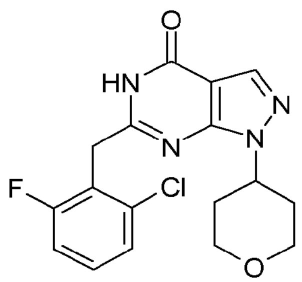
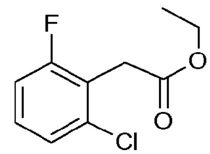
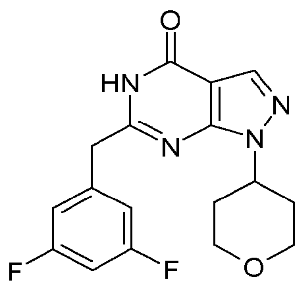
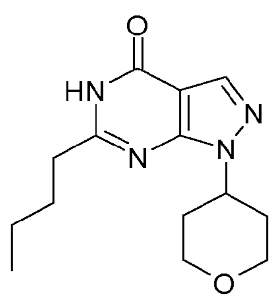
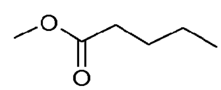
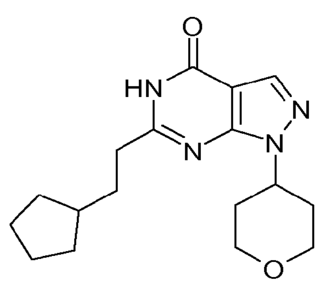
HPLC-MS (Method1): R_t: 1.08 min

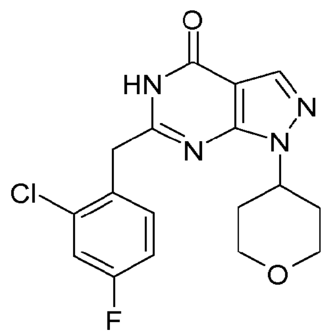
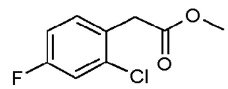
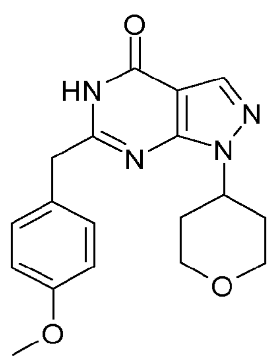
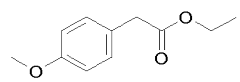
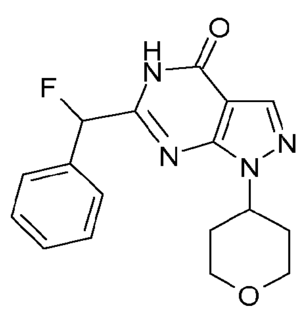
MS (ESI pos): m/z = 331 $(M+H)^+$

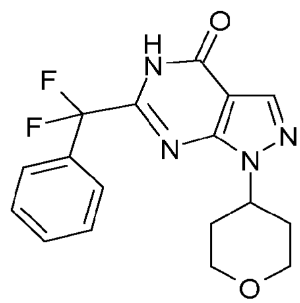
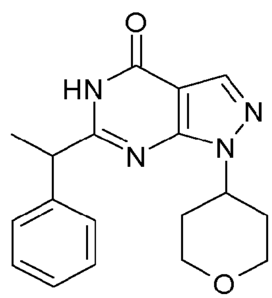
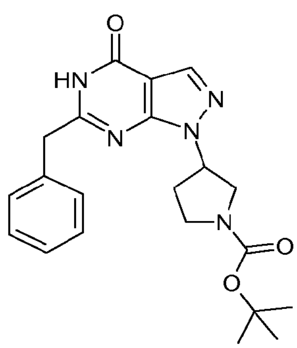
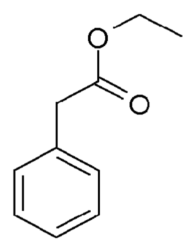
The following examples were synthesized in analogy to the preparation of Example 1, using the corresponding pyrazoles and esters or nitriles as starting materials

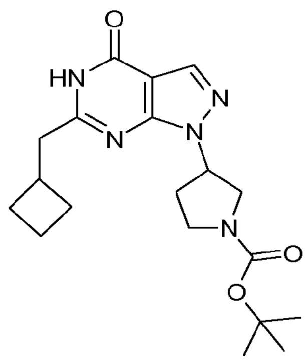
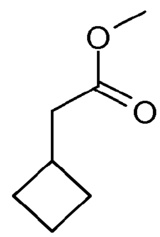
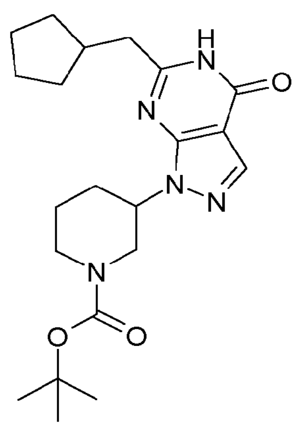
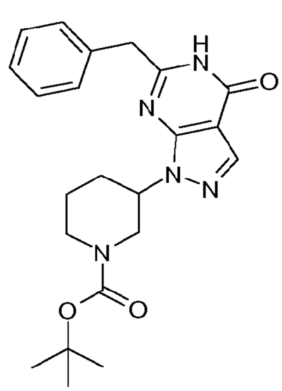
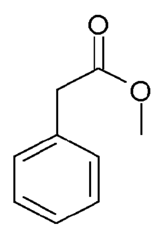
	structure	starting material: pyrazole	starting material: ester or nitrile	R_t [min]	MS (ESI-APCI pos/neg, m/z)

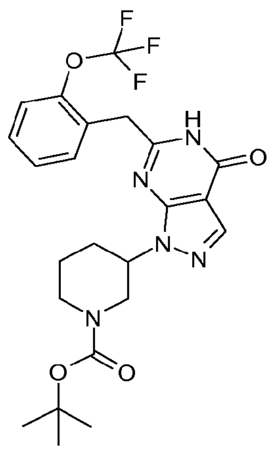
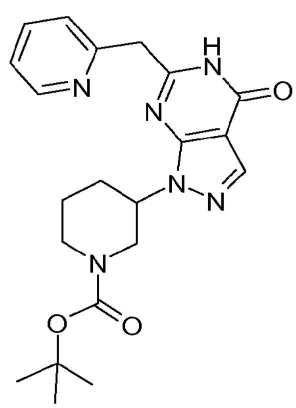
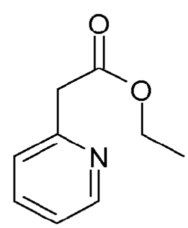
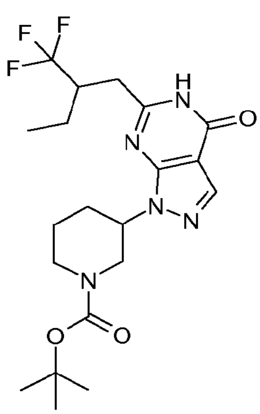
	structure	starting material: pyrazole	starting material: ester or nitrile	R_t [min]	MS (ESI-APCI pos/neg, m/z)
Exp. 2		Example 11B		1.27 (Method 1)	325 $(M+H)^+$
Exp. 3		Example 11B		1.22 (Method 1)	291 $(M+H)^+$
Exp. 4		Example 11B	Example 5Y	1.23 (Method 1)	345/347 (Cl) $(M+H)^+$
Exp. 5		Example 11B	Example 5U	1.29 (Method 1)	389/91 (Br) $(M+H)^+$

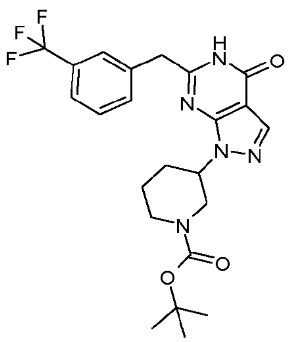
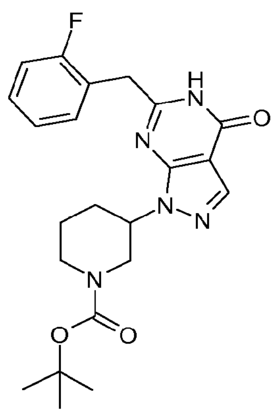
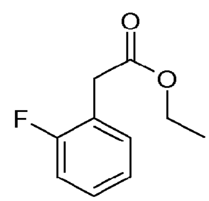
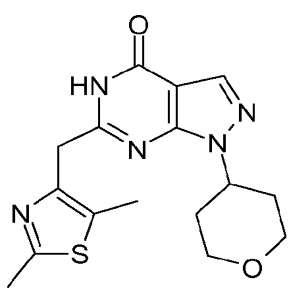
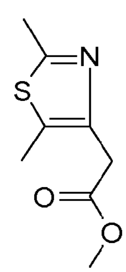
	structure	starting material: pyrazole	starting material: ester or nitrile	R_t [min]	MS (ESI-APCI pos/neg, m/z)
Exp. 6		Example 11B		1.28 (Method 1)	363/65 (Cl) $(M+H)^+$
Exp. 7		Example 11B	Example 5W	1.22 (Method 1)	345 $(M-H)^-$
Exp. 8		Exp. 11B		1.14 (Method 1)	277 $(M+H)^+$
Exp. 9		Exp. 11B	Example 5X	1.37 (Method 1)	317 $(M+H)^+$

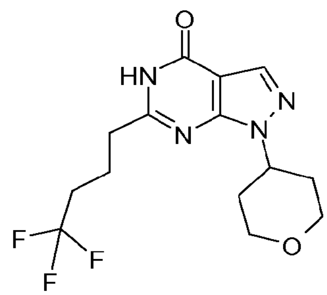
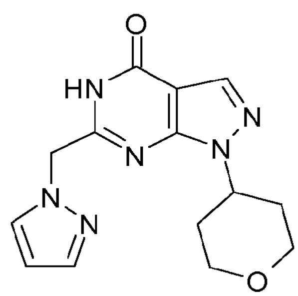
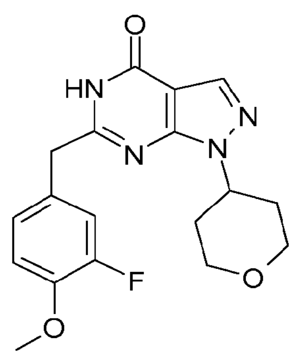
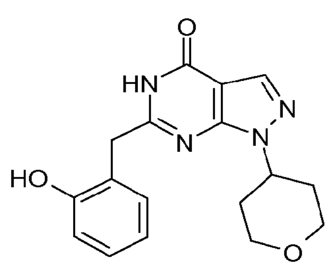
	structure	starting material: pyrazole	starting material: ester or nitrile	R_t [min]	MS (ESI-APCI pos/neg, m/z)
Exp. 10		Exp. 11B		1.30 (Method 1)	361/63 (Cl) $(M+H)^+$
Exp. 11		Exp. 11B		1.18 (Method 1)	341 $(M+H)^+$
Exp. 12 racem. mixture		Exp. 11B	Example 5AA	1.44 (Method 1)	329 $(M+H)^+$

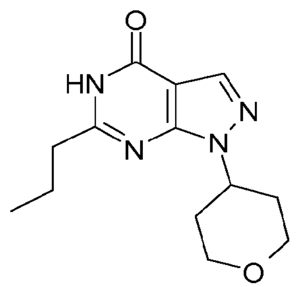
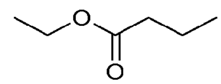
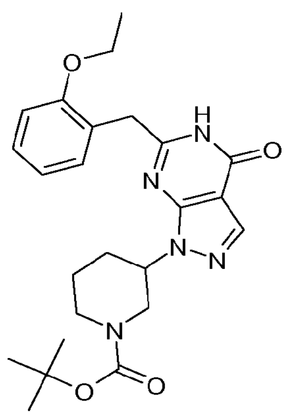
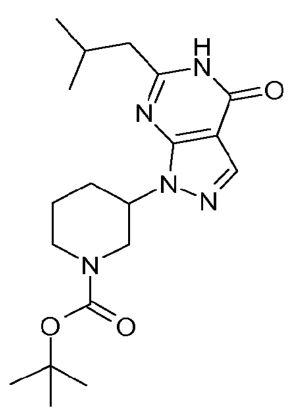
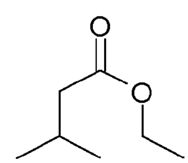
	structure	starting material: pyrazole	starting material: ester or nitrile	R_t [min]	MS (ESI-APCI pos/neg, m/z)
Exp. 13		Exp. 11B	Example 5AB	1.26 (Method 1)	347 $(M+H)^+$
Exp. 14 racem. mixture		Exp. 11B	Example 5AF	1.28 (Method 1)	325 $(M+H)^+$
Exp. 15 racem. mixture		Exp. 11A		1.49 (Method1)	396 $(M+H)^+$

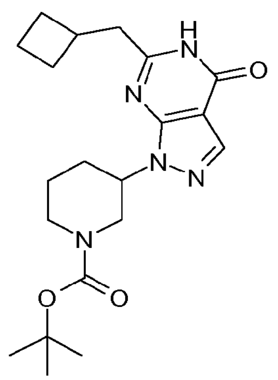
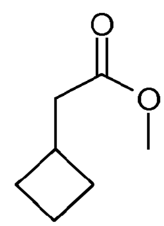
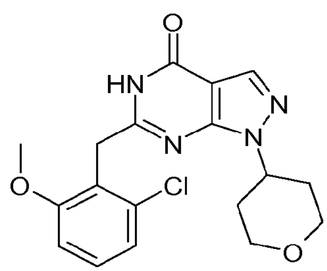
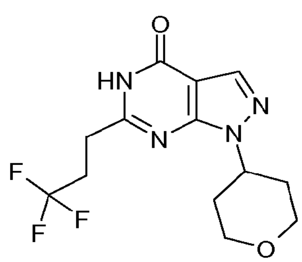
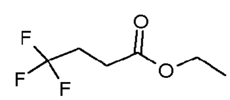
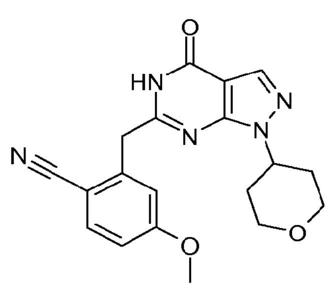
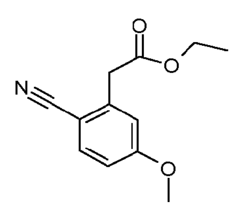
	structure	starting material: pyrazole	starting material: ester or nitrile	R_t [min]	MS (ESI-APCI pos/neg, m/z)
Exp. 16 racem. mixture		Exp. 11A		1.49 (Method 1)	374 $(M+H)^+$
Exp. 17 racem. mixture		Exp. 11D	Example 5AC	1.65 (Method 1)	402 $(M+H)^+$
Exp. 18 racem. mixture		Exp. 11D		1.55 (Method 1)	408 $(M+H)^+$

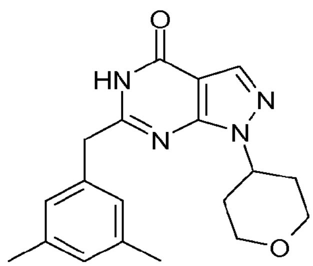
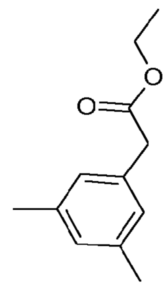
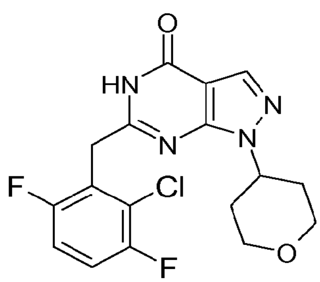
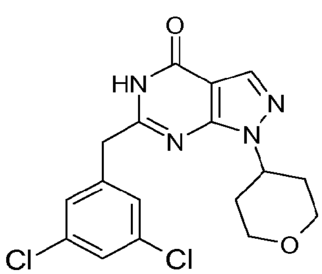
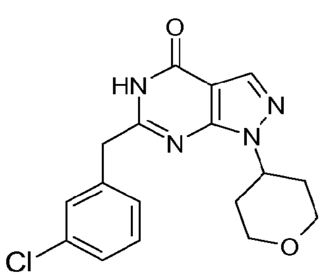
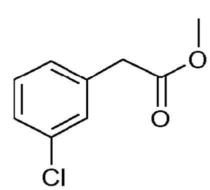
	structure	starting material: pyrazole	starting material: ester or nitrile	R_t [min]	MS (ESI-APCI pos/neg, m/z)
Exp. 19 racem. mixture		Exp. 11D	Example 5AE	1.67 (Method1)	494 $(M+H)^+$
Exp. 20 racem. mixture		Exp. 11D		1.13 (Method 1)	411 $(M+H)^+$
Exp. 21 racem. mixture		Exp. 11D	Example 5T	1.63 (Method 1)	444 $(M+H)^+$

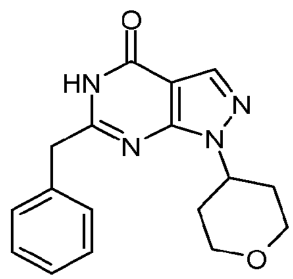
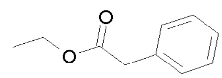
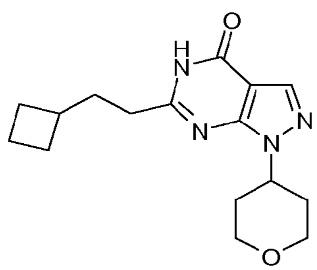
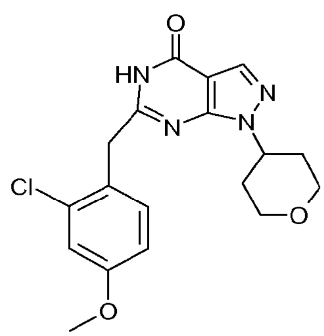
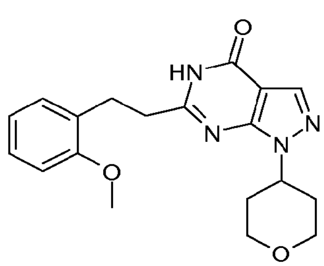
	structure	starting material: pyrazole	starting material: ester or nitrile	R_t [min]	MS (ESI-APCI pos/neg, m/z)
Exp. 22 racem. mixture		Exp. 11D	Example 5AH	1.66 (Method 1)	478 $(M+H)^+$
Exp. 23 racem. mixture		Exp. 11D		1.53 (Method 1)	428 $(M+H)^+$
Exp. 24		Exp. 11B		0.91 (Method 1)	346 $(M+H)^+$

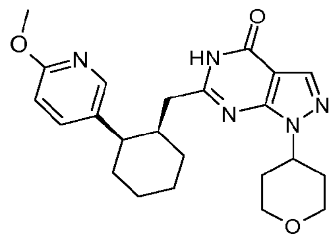
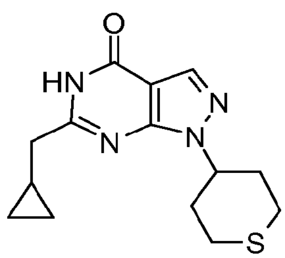
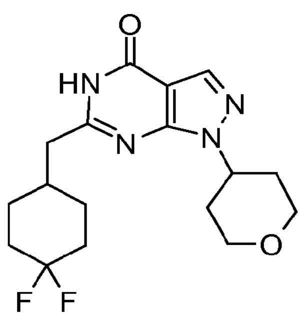
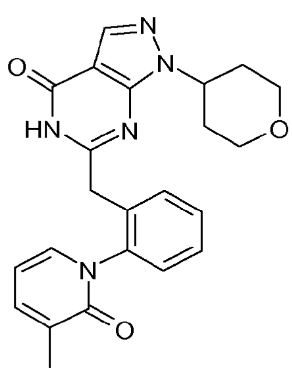
	structure	starting material: pyrazole	starting material: ester or nitrile	R_t [min]	MS (ESI-APCI pos/neg, m/z)
Exp. 25		Exp. 11B	Example 5AI	1.17 (Method 1)	331 $(M+H)^+$
Exp. 26		Exp. 11B	Example 5AN	0.87 (Method 1)	301 $(M+H)^+$
Exp. 27		Exp. 11B	Example 5AJ	1.17 (Method 1)	359 $(M+H)^+$
Exp. 28		Exp. 11B	Example 5AM	1.08 (Method 1)	327 $(M+H)^+$

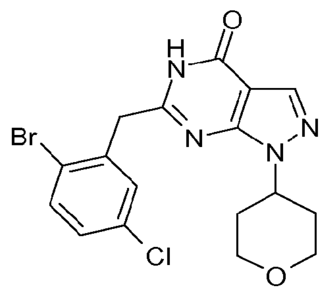
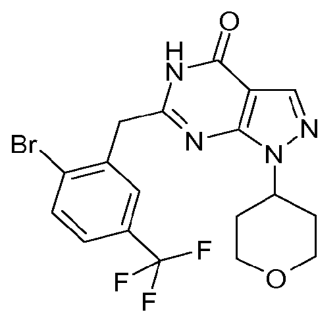
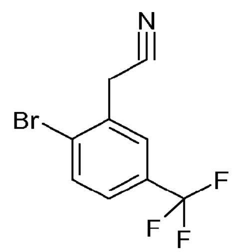
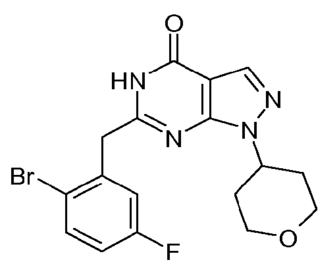
	structure	starting material: pyrazole	starting material: ester or nitrile	R_t [min]	MS (ESI-APCI pos/neg, m/z)
Exp. 29		Exp. 11B		1.02 (Method 1)	263 $(M+H)^+$
Exp. 30 racem. mixture		Exp. 11D	Example 5AK	1.63 (Method 1)	454 $(M+H)^+$
Exp. 31 racem. mixture		Exp. 11D		1.51 (Method 1)	376 $(M+H)^+$

	structure	starting material: pyrazole	starting material: ester or nitrile	R_t [min]	MS (ESI-APCI pos/neg, m/z)
Exp. 32 racem. mixture		Exp. 11D		1.56 (Method 1)	388 $(M+H)^+$
Exp. 33		Exp. 11B	Example 5AO	1.29 (Method 1)	375/377 (Cl) $(M+H)^+$
Exp. 34		Exp. 11B		1.11 (Method 1)	317 $(M+H)^+$
Exp. 35		Exp. 11B		1.17 (Method 1)	366 $(M+H)^+$

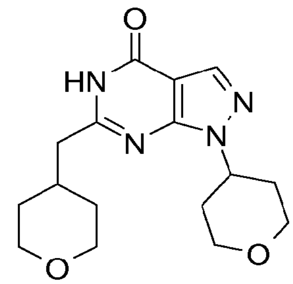
	structure	starting material: pyrazole	starting material: ester or nitrile	R_t [min]	MS (ESI-APCI pos/neg, m/z)
Exp. 36		Exp. 11B		1.36 (Method 1)	339 $(M+H)^+$
Exp. 37		Exp. 11B	Example 5AL	1.3 (Method 1)	381/383 (Cl) $(M+H)^+$
Exp. 38		Exp. 11B	Example 5Z	1.44 (Method 1)	379/381/383 (Cl_2) $(M+H)^+$
Exp. 39		Exp. 11B		1.28 (Method 1)	345/347 (Cl) $(M+H)^+$

	structure	starting material: pyrazole	starting material: ester or nitrile	R_t [min]	MS (ESI-APCI pos/neg, m/z)
Exp. 40		Exp. 11B		1.16 (Method 1)	311 $(M+H)^+$
Exp. 40-1		Exp. 11B	Exp. 5ALC	1.30 (Method 1)	303 $(M+H)^+$
Exp. 40-2		Exp. 11B	Example 5ALB	1.31 (Method 1)	375 $(M+H)^+$
Exp. 40-3		Exp. 11B	Example 5ALD	1.25 (Method 1)	355 $(M+H)^+$

	structure	starting material: pyrazole	starting material: ester or nitrile	R_t [min]	MS (ESI-APCI pos/neg, m/z)
Exp. 40-4 cis, racem. mixture		Exp. 11B	Exp. 5HA	1.18 (Method 1)	424 $(M+H)^+$
Exp. 40-5		Exp. 11IC	Exp. 5ALA	1.24 (Method 1)	291 $(M+H)^+$
Exp. 40-6		Exp. 11B	Example 5TA	1.22 (Method 1)	353 $(M+H)^+$
Exp. 40-7		Exp. 11B	Example 5AP	1.35 (Method 1)	418 $(M+H)^+$

	structure	starting material: pyrazole	starting material: ester or nitrile	R_t [min]	MS (ESI-APCI pos/neg, m/z)
Exp. 40-8		Exp. 11B	Example 5ALF	1.78 (Method 5)	423/425/427 $(M+H)^+$ (Cl/Br)
Exp. 40-9		Exp. 11B		1.81 (Method 5)	458/460 $(M+H)^+$ (Br)
Exp. 40-10		Exp. 11B	Example 5ALG	1.33 (Method 1)	407/409 $(M+H)^+$ (Br)

Example 41



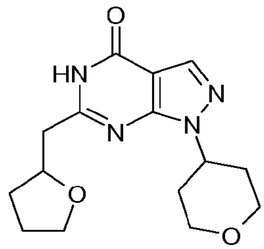
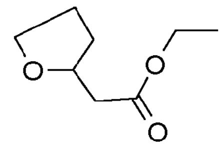
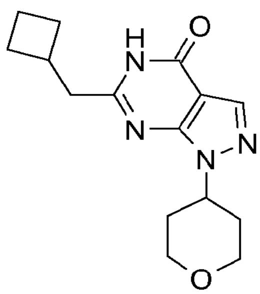
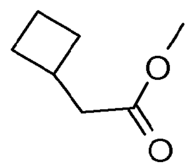
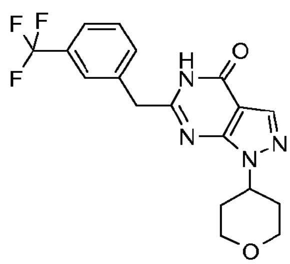
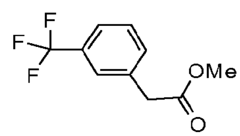
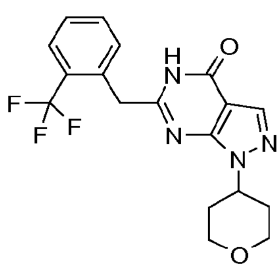
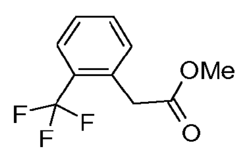
80 mg (0.38 mmol) of Example 11B were dissolved in 1 mL of absolute ethanol, 262 mg (1.52 mmol) of ethyl tetrahydropyran-4-yl-acetate, and 45.1 mg (1.10 mmol) of sodium hydride (60 % suspension in mineral oil) were added. The reaction mixture was heated to 150°C for 40 min in a microwave oven. Cooling to 20°C was followed by evaporation of the solvent under reduced pressure. The residue was treated with water (10 mL), acidified with HCl (10 % in water) and extracted two times with dichloromethane (2 mL). The organic layer was dried over sodium sulphate, filtered and the filtrate was concentrated under reduced pressure. The residue was triturated with ether to give 65 mg (53.7 %) of the product as a white solid.

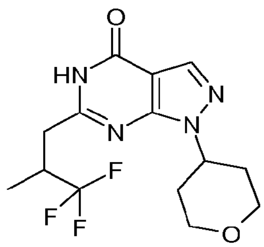
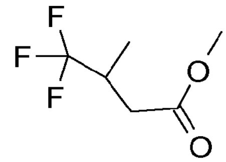
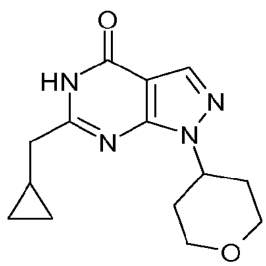
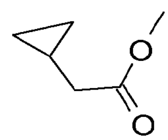
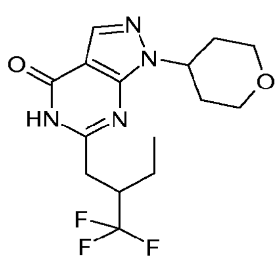
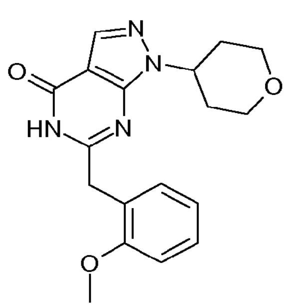
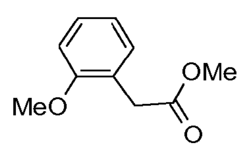
HPLC-MS (Method Grad_C8_NH_4COOH): R_t: 1.89 min

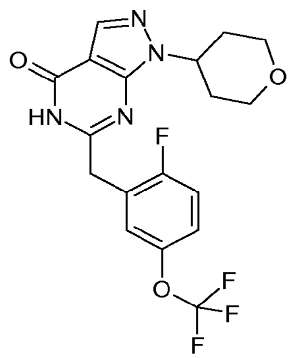
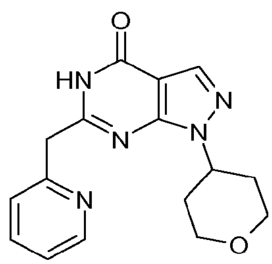
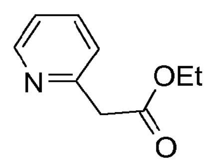
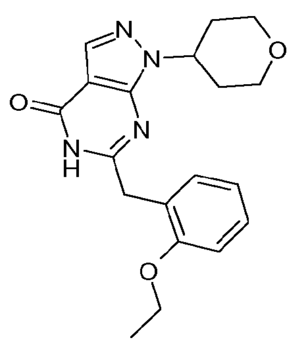
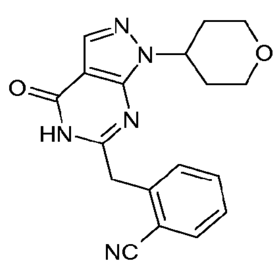
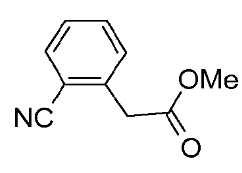
MS (ESI pos): m/z = 319 $(M+H)^+$.

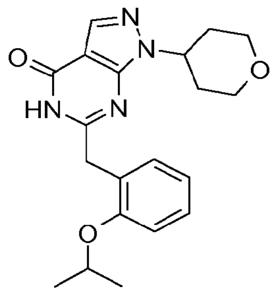
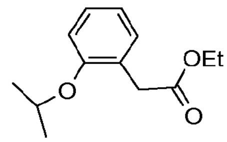
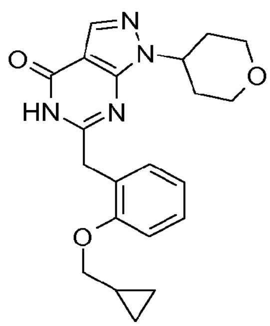
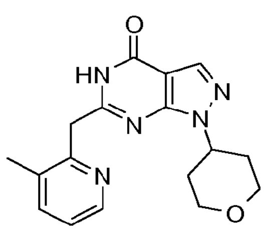
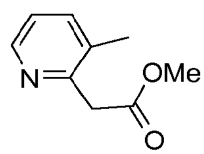
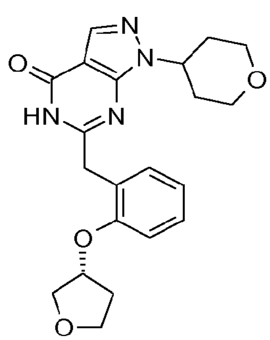
The following examples were synthesized in analogy to the preparation of Example 41, using the corresponding pyrazolyl-carboxamides and esters as starting materials.

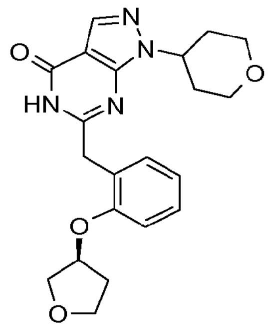
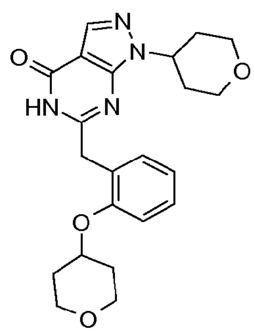
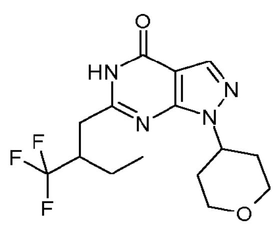
	Structure	pyrazolyl -carbox-amide	Ester	R_t [min]	MS (ESI-APCI, m/z)

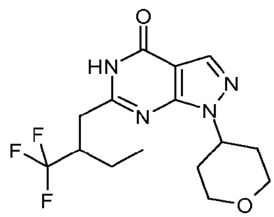
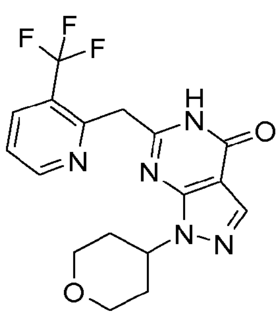
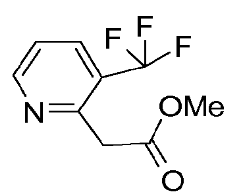
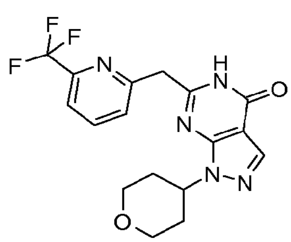
	Structure	pyrazolyl-carbox-amide	Ester	R_t [min]	MS (ESI-APCI, m/z)
Exp. 42 racem. mixture		Exp. 11B		2.02 (Method Grad_C8_ NH_4COOH)	305 $(M+H)^+$
Exp. 43		Exp. 11B		2.40 (Method Grad_C8_ NH_4COOH)	289 $(M+H)^+$
Exp. 44		Exp. 11B		3.06 (Method Grad_C8_ NH_4COOH)	379 $(M+H)^+$
Exp. 45		Exp. 11B		3.04 (Method Grad_C8_ NH_4COOH)	379 $(M+H)^+$

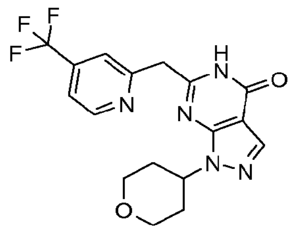
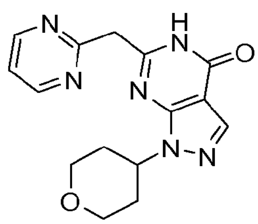
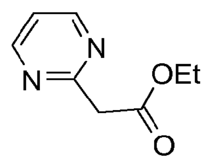
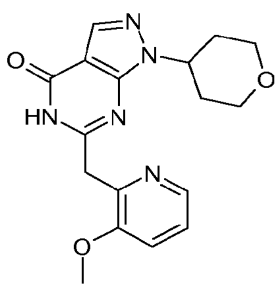
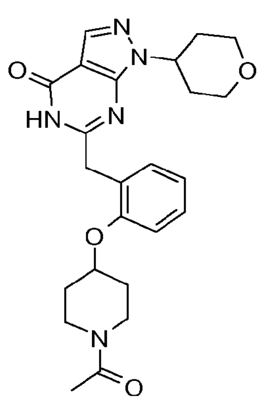
	Structure	pyrazolyl-carbox-amide	Ester	R_t [min]	MS (ESI-APCI, m/z)
Exp. 46 racem. mixture		Exp. 11B		2.77 (Method Grad_C8_ NH_4COOH)	331 $(M+H)^+$
Exp. 47		Exp. 11B		2.21 (Method Grad_C8_ NH_4COOH)	275 $(M+H)^+$
Exp. 48 racem. mixture		Exp. 11B	Exp. 5T	2.84 (Method Grad_C8_ NH_4COOH)	345 $(M+H)^+$
Exp. 49		Exp. 11B		2.57 (Method Grad_C8_ NH_4COOH)	341 $(M+H)^+$

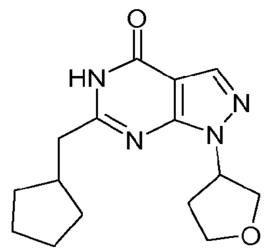
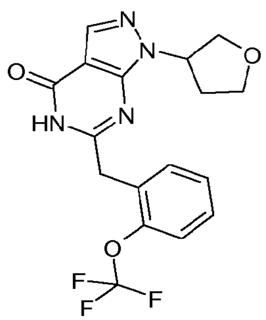
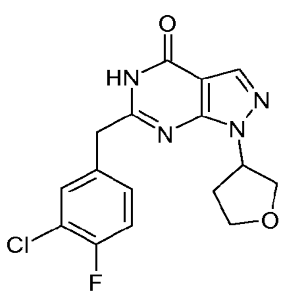
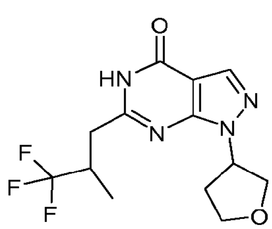
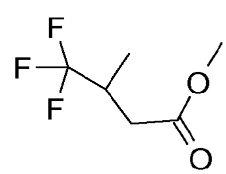
	Structure	pyrazolyl-carbox-amide	Ester	R_t [min]	MS (ESI-APCI, m/z)
Exp. 50		Exp. 11B	Exp. 5E	3.02 (Method Grad_C8_ NH_4COOH)	413 $(M+H)^+$
Exp. 51		Exp. 11B		5.97 (Method 1E hydro)	312 $(M+H)^+$
Exp. 52		Exp. 11B	Exp. 5AK	2.75 (Method Grad_C8_ NH_4COOH)	355 $(M+H)^+$
Exp. 53		Exp. 11B		2.75 (Method Grad_C8_ NH_4COOH)	336 $(M+H)^+$

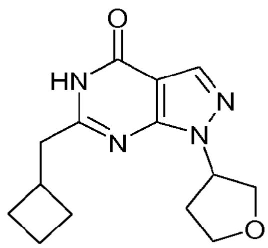
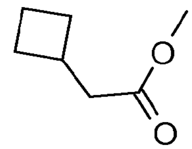
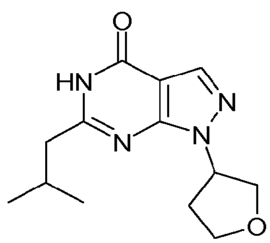
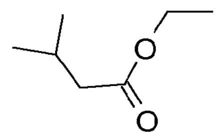
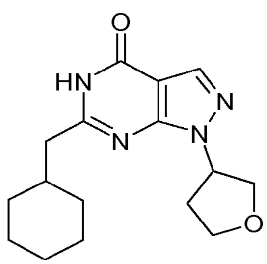
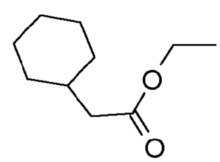
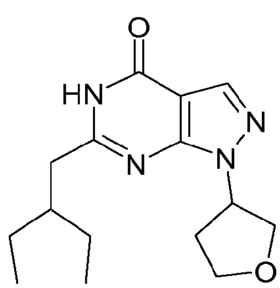
	Structure	pyrazolyl -carbox-amide	Ester	R_t [min]	MS (ESI-APCI, m/z)
Exp. 54		Exp. 11B		3.15 (Method Grad_C8_ NH_4COOH)	369 $(M+H)^+$
Exp. 55		Exp. 11B	Exp. 5K	3.21 (Method Grad_C8_ NH_4COOH)	381 $(M+H)^+$
Exp. 56		Exp. 11B		6.52 (Method 1E hydro)	326 $(M+H)^+$
Exp. 57 Enantio -mer R		Exp. 11B	Exp. 5M	2.64 (Method Grad_C8_ NH_4COOH)	397 $(M+H)^+$

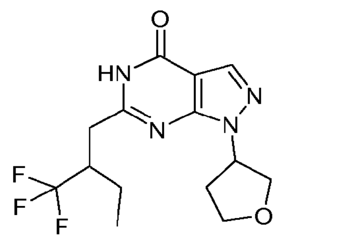
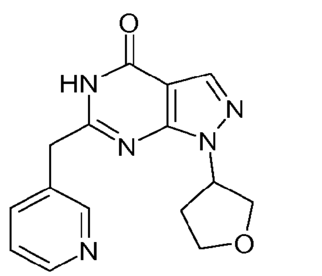
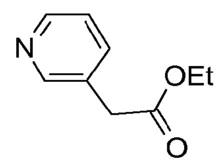
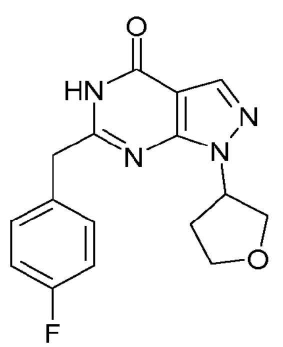
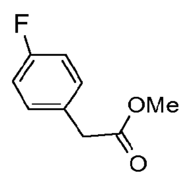
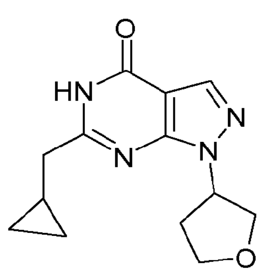
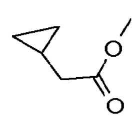
	Structure	pyrazolyl-carbox-amide	Ester	R_t [min]	MS (ESI-APCI, m/z)
Exp. 58 Enantio-mer S		Exp. 11B	Exp. 5L	2.64 (Method Grad_C8_ NH_4COOH)	397 $(M+H)^+$
Exp. 60		Exp. 11B	Exp. 5O	2.78 (Method Grad_C8_ NH_4COOH)	411 $(M+H)^+$
Exp. 61 Enantio-mer A		Exp. 11B	Exp. 5A	2.68 (Method Grad_C8_ NH_4COOH) 15.32 (Chiral 1)	345 $(M+H)^+$

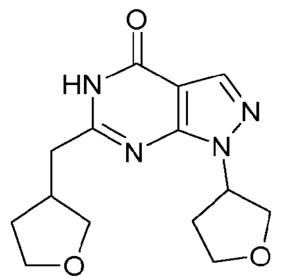
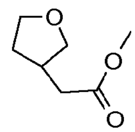
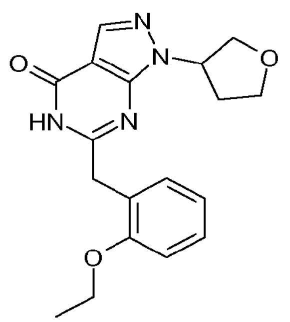
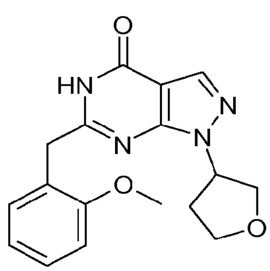
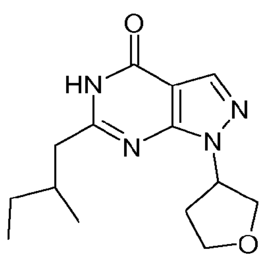
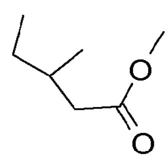
	Structure	pyrazolyl-carbox-amide	Ester	R_t [min]	MS (ESI-APCI, m/z)
Exp. 62 Enantio-mer B		Exp. 11B	Exp. 5D	2.68 (Method Grad_C8_ NH_4COOH) 18.74 (Chiral 1)	345 $(M+H)^+$
Exp. 63		Exp. 11B		9.37 (Method 2F)	380 $(M+H)^+$
Exp. 64		Exp. 11B	Exp. 5S	6.75 (Method 1E hydro)	380 $(M+H)^+$

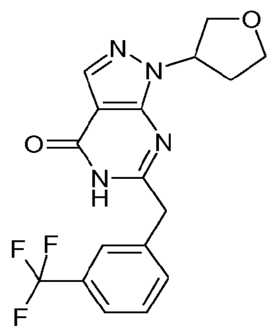
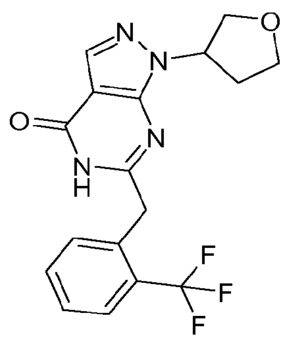
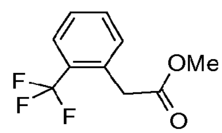
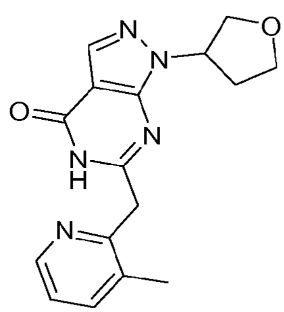
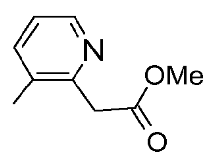
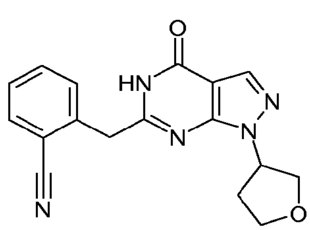
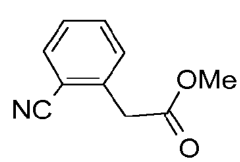
	Structure	pyrazolyl-carboxamide	Ester	R_t [min]	MS (ESI-APCI, m/z)
Exp. 65		Exp. 11B	Exp. 5R	9.45 (Method 2F)	380 $(M+H)^+$
Exp. 66		Exp. 11B		6.70 (Method 2F)	313 $(M+H)^+$
Exp. 67		Exp. 11B	Exp. 5Q	2.38 (Method Grad_C8_ NH_4COOH)	342 $(M+H)^+$
Exp. 68		Exp. 11B	Exp. 5I	1.95 (Method Grad_C8_ NH_4COOH)	452 $(M+H)^+$

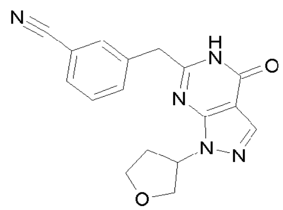
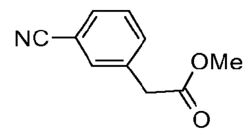
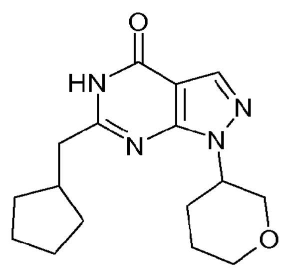
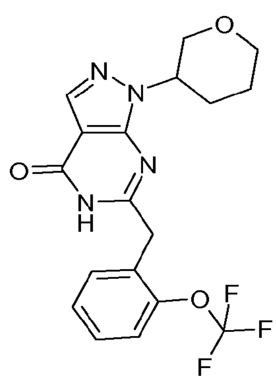
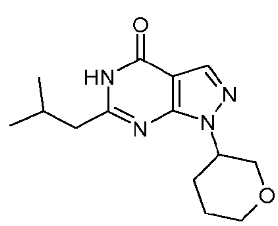
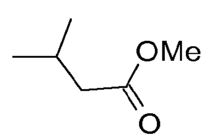
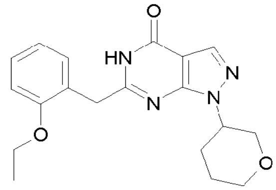
	Structure	pyrazolyl -carbox- amide	Ester	R_t [min]	MS (ESI-APCI, m/z)
Exp. 69 racem. mixture		Exp. 11E	Exp. 5AC	7.30 (Method 1E)	289 $(M+H)^+$
Exp. 70 racem. mixture		Exp. 11E	Exp. 5AE	7.70 (Method 1E fusion)	381 $(M+H)^+$
Exp. 71 racem. mixture		Exp. 11E	Exp. 5F	7.68 (Method 1E fusion)	349 $(M+H)^+$
Exp. 72 mixture of stereois omers		Exp. 11E		9.82 (Method 2F)	317 $(M+H)^+$

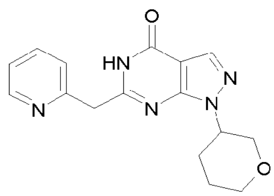
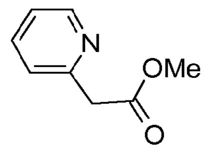
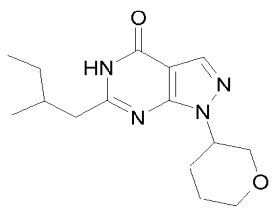
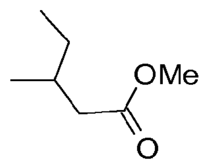
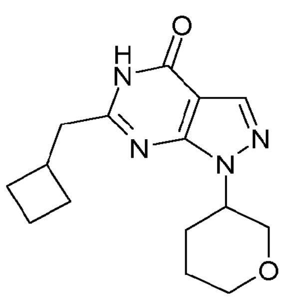
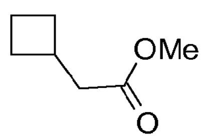
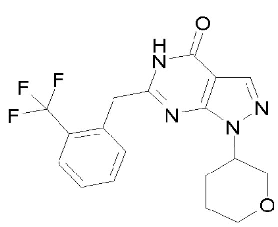
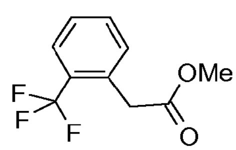
	Structure	pyrazolyl-carbox-amide	Ester	R_t [min]	MS (ESI-APCI, m/z)
Exp. 73 racem. mixture		Exp. 11E		9.44 (Method 2F)	275 $(M+H)^+$
Exp. 74 racem. mixture		Exp. 11E		8.89 (Method 2F)	263 $(M+H)^+$
Exp. 75 racem. mixture		Exp. 11E		10.69 (Method 2F)	303 $(M+H)^+$
Exp. 76 racem. mixture		Exp. 11E	Exp. 5H	10.57 (Method 2F)	291 $(M+H)^+$

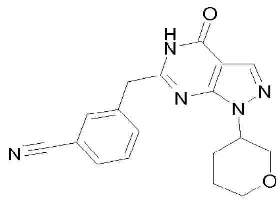
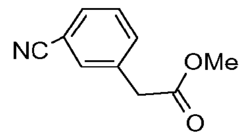
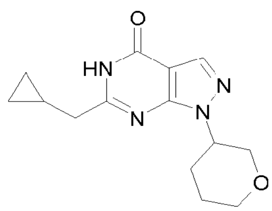
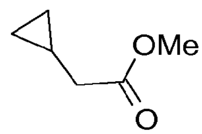
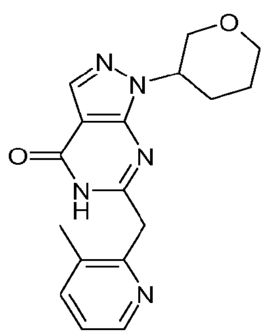
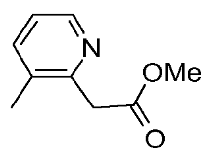
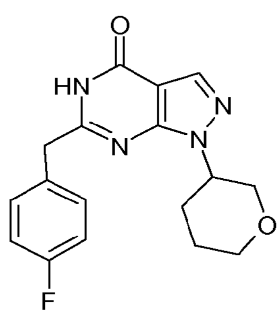
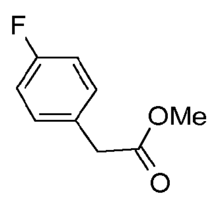
	Structure	pyrazolyl-carbox-amide	Ester	R_t [min]	MS (ESI-APCI, m/z)
Exp. 77 mixture of stereoisomers		Exp. 11E	Exp. 5T	10.55 (Method 2F)	331 $(M+H)^+$
Exp. 78 racem. mixture		Exp. 11E		4.83 (Method 1E Hydro)	298 $(M+H)^+$
Exp. 79 racem. mixture		Exp. 11E		7.10 (Method 1E fusion)	315 $(M+H)^+$
Exp. 80 racem. mixture		Exp. 11E		5.97 (Method 1E fusion)	261 $(M+H)^+$

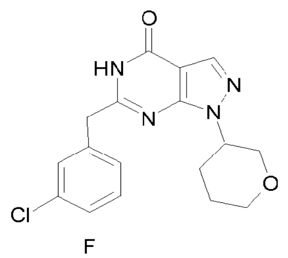
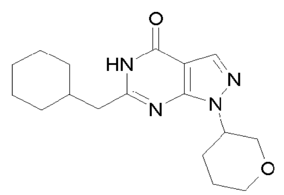
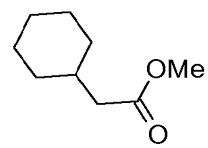
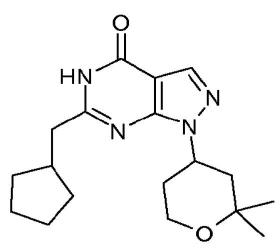
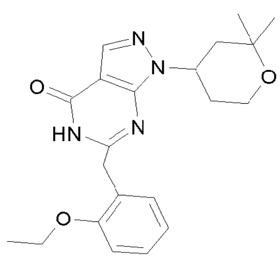
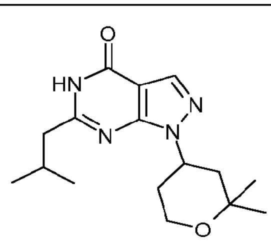
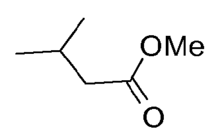
	Structure	pyrazolyl-carbox-amide	Ester	R_t [min]	MS (ESI-APCI, m/z)
Exp. 81 mixture of stereoisomers		Exp. 11E		4.73 (Method 1E hydro)	291 $(M+H)^+$
Exp. 82 racem. mixture		Exp. 11E	Exp. 5AK	7.37 (Method 1E hydro)	341 $(M+H)^+$
Exp. 83 racem. mixture		Exp. 11E	Exp. 5AD	6.85 (Method 1E hydro)	327 $(M+H)^+$
Exp. 84 mixture of stereoisomers		Exp. 11E		6.88 (Method 1E hydro)	277 $(M+H)^+$

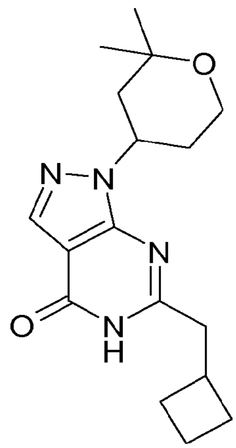
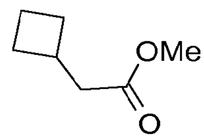
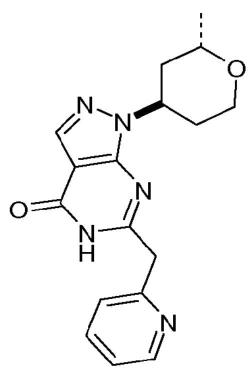
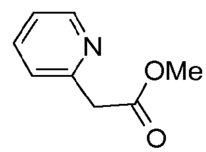
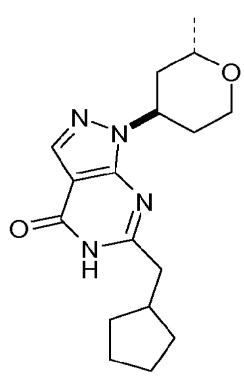
	Structure	pyrazolyl-carbox-amide	Ester	R_t [min]	MS (ESI-APCI, m/z)
Exp. 85 racem. mixture		Exp. 11E	Exp. 5AH	7.93 (Method 1E hydro)	365 $(M+H)^+$
Exp. 86 racem. mixture		Exp. 11E		10.93 (Method 2F)	365 $(M+H)^+$
Exp. 87 racem. mixture		Exp. 11E		5.43 (Method 1E hydro)	312 $(M+H)^+$
Exp. 88 racem. mixture		Exp. 11E		5.43 (Method 1E hydro)	312 $(M+H)^+$

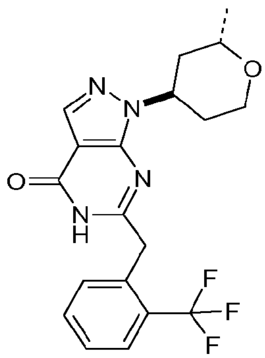
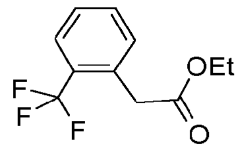
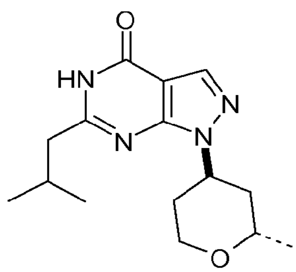
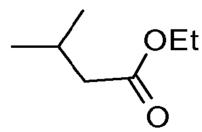
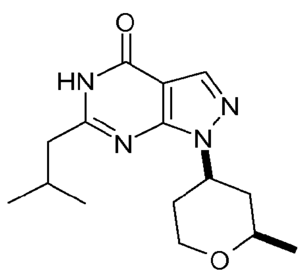
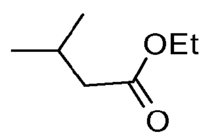
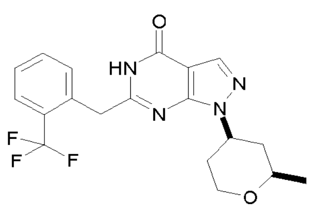
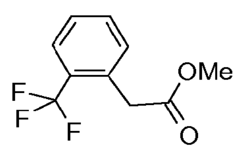
	Structure	pyrazolyl -carbox-amide	Ester	R_t [min]	MS (ESI-APCI, m/z)
Exp. 89 racem. mixture		Example 11E		5.28 (Method 1E hydro)	322 $(M+H)^+$
Exp. 90 racem. mixture		Exp. 11F	Exp. 5AC	8 (Method 1E hydro)	303 $(M+H)^+$
Exp. 91 racem. mixture		Exp. 11F	Exp. 5AE	8.45 (Method 1E hydro)	395 $(M+H)^+$
Exp. 92 racem. mixture		Exp. 11F		6.93 (Method 1E hydro)	277 $(M+H)^+$
Exp. 93 racem. mixture		Exp. 11F	Exp. 5AK	8.20 (Method	355 $(M+H)^+$

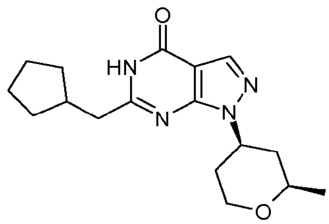
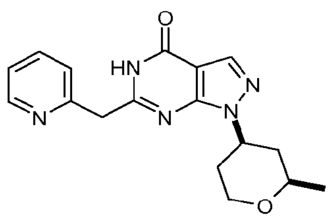
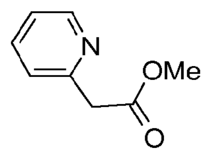
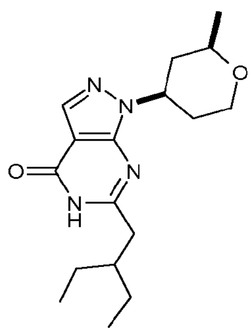
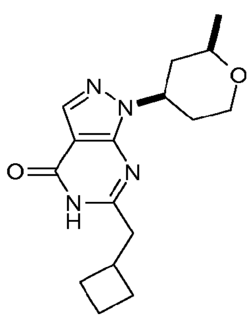
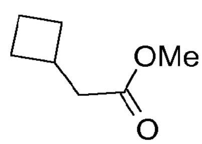
	Structure	pyrazolyl-carbox-amide	Ester	R_t [min]	MS (ESI-APCI, m/z)
				1E hydro)	
Exp. 94 racem. mixture		Exp. 11F		6.28 (Method 1E hydro)	312 $(M+H)^+$
Exp. 95 mixture of stereoisomers		Exp. 11F		7.70 (Method 1E hydro)	291 $(M+H)^+$
Exp. 96 racem. mixture		Exp. 11F		7.33 (Method 1E hydro)	289 $(M+H)^+$
Exp. 97 racem. mixture		Exp. 11F		8.17 (Method 1E hydro)	379 $(M+H)^+$

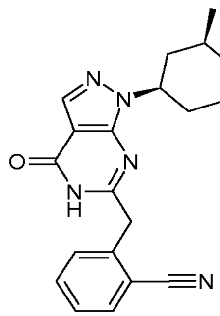
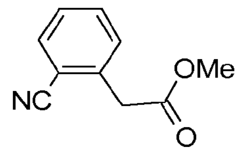
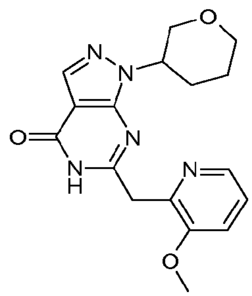
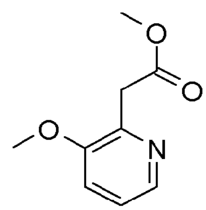
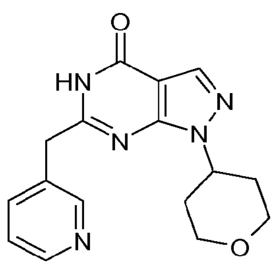
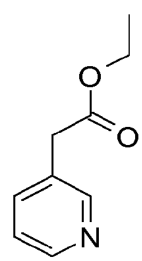
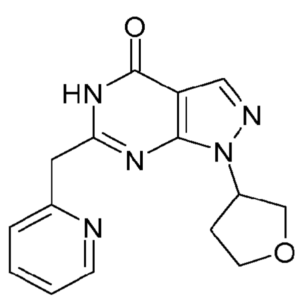
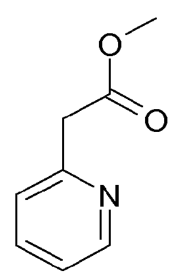
	Structure	pyrazolyl-carbox-amide	Ester	R_t [min]	MS (ESI-APCI, m/z)
Exp. 98 racem. mixture		Exp. 11F		6.80 (Method 1E hydro)	336 $(M+H)^+$
Exp. 99 racem. mixture		Exp. 11F		6.43 (Method 1E hydro)	275 $(M+H)^+$
Exp. 100 racem. mixture		Exp. 11F		2.38 (Method 2F)	326 $(M+H)^+$
Exp. 101 racem. mixture		Exp. 11F		7.52 (Method 1E hydro)	329 $(M+H)^+$

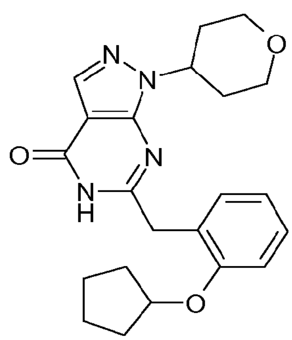
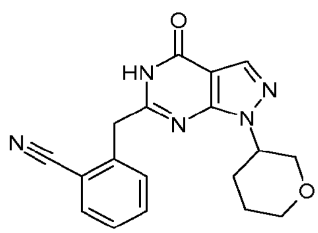
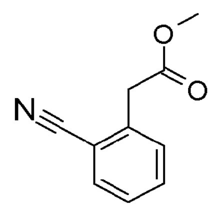
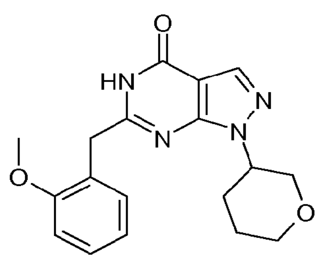
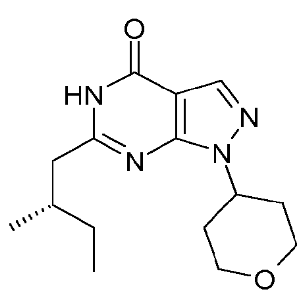
	Structure	pyrazolyl-carbox-amide	Ester	R_t [min]	MS (ESI-APCI, m/z)
Exp. 102 racem. mixture		Exp. 11F	Exp. 5F	8.28 (1E hydro)	363 $(M+H)^+$
Exp. 103 racem. mixture		Exp. 11F		8.70 (Method 1E hydro)	317 $(M+H)^+$
Exp. 104 racem. mixture		Exp. 11G	Exp. 5AC	8.57 (Method 1E hydro)	331 $(M+H)^+$
Exp. 105 racem. mixture		Exp. 11G	Exp. 5AK	8.62 (Method 1E hydro)	383 $(M+H)^+$
Exp. 106 racem. mixture		Exp. 11G	Methyliso-valerate 	7.58 (Method 1E hydro)	305 $(M+H)^+$

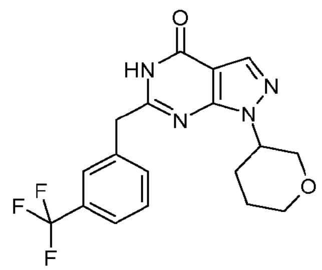
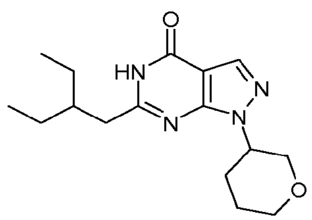
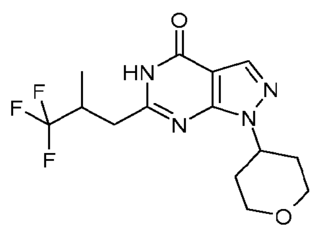
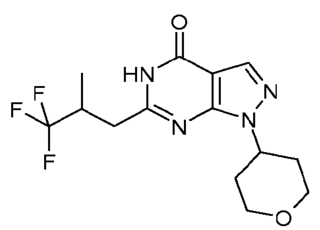
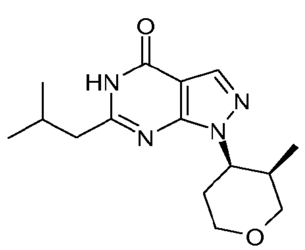
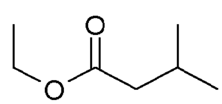
	Structure	pyrazolyl -carbox-amide	Ester	R_t [min]	MS (ESI-APCI, m/z)
Exp. 108 racem. mixture		Exp. 11G	Cyclobutyl-acetic acid methyl ester 	7.93 (Method 1E)	317 $(M+H)^+$
Exp. 111 trans; racem. mixture		Exp. 11H		2.05 (Method 2F)	326 $(M+H)^+$
Exp. 112 trans; racem. mixture		Exp. 11H	Exp. 5AC	8.25 (Method 2F)	317 $(M+H)^+$

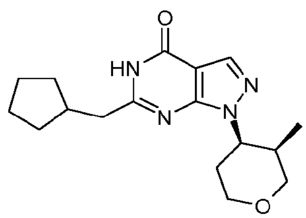
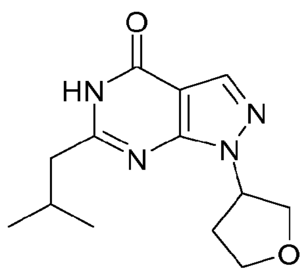
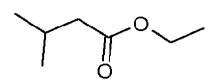
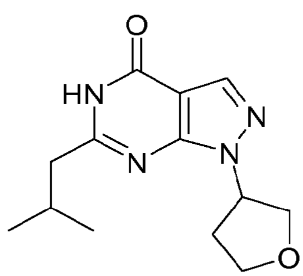
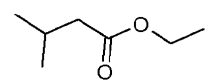
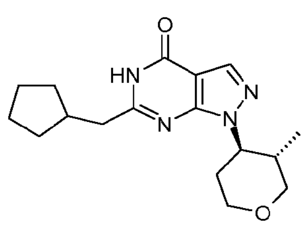
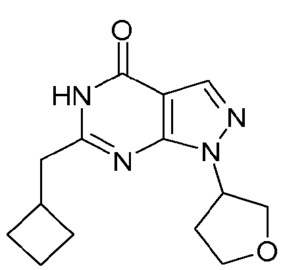
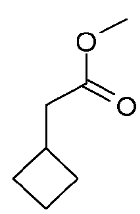
	Structure	pyrazolyl-carbox-amide	Ester	R_t [min]	MS (ESI-APCI, m/z)
Exp. 113 trans; racem. mixture		Exp. 11H		8.42 (Method 1E hydro)	393 $(M+H)^+$
Exp. 114 trans; racem. mixture		Exp. 11H		7.15 (Method 1E hydro)	291 $(M+H)^+$
Exp. 115 cis; racem. mixture		Exp. 11I		9.90 (Method 2F)	291 $(M+H)^+$
Exp. 116 cis; racem. mixture		Exp. 11I		8.18 (Method 1E hydro)	393 $(M+H)^+$

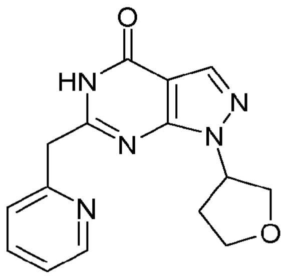
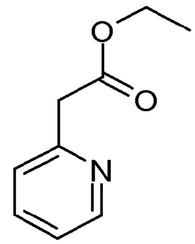
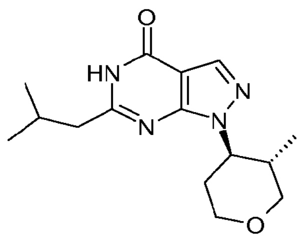
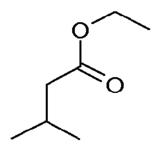
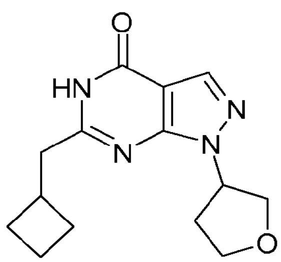
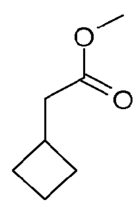
	Structure	pyrazolyl-carbox-amide	Ester	R_t [min]	MS (ESI-APCI, m/z)
Exp. 117 cis; racem. mixture		Exp. 11I	Exp. 5AC	7.98 (Method 1E hydro)	317 $(M+H)^+$
Exp. 118 cis; racem. mixture		Exp. 11I		5.80 (Method 1E hydro)	326 $(M+H)^+$
Exp. 119 cis; racem. mixture		Exp. 11I	Exp. 5H	8.42 (Method 1E hydro)	319 $(M+H)^+$
Exp. 120 cis; racem. mixture		Exp. 11I		7.33 (Method 1E hydro)	303 $(M+H)^+$

	Structure	pyrazolyl-carbox-amide	Ester	R_t [min]	MS (ESI-APCI, m/z)
Exp. 121 cis; racem. mixture		Exp. 11I		9.91 (Method 2F)	350 $(M+H)^+$
Exp. 122 racem. mixture		Exp. 11F		6.95 (Method 2F)	342 (M+H)+
Exp. 123		Exp. 11B		2.12 (Method Grad_C8_ NH_4COOH)	312 $(M+H)^+$
Exp. 124 racem. mixture		Exp. 11E		4.98 (Method 1E hydro)	298 $(M+H)^+$

	Structure	pyrazolyl -carbox-amide	Ester	R_t [min]	MS (ESI-APCI, m/z)
Exp. 125		Exp. 11B	Exp. 5P	8.72 (Method 1E hydro)	395 $(M+H)^+$
Exp. 126 racem. mixture		Exp. 11F		9.72 (Method 2F)	336 $(M+H)^+$
Exp. 127 racem. mixture		Exp. 11F	Exp. 5AB	7.62 (Method 1E hydro)	341 $(M+H)^+$
Exp. 128 Enantio -mer S		Exp. 11B	Exp. 5G	9.83 (Method 2F)	291 $(M+H)^+$

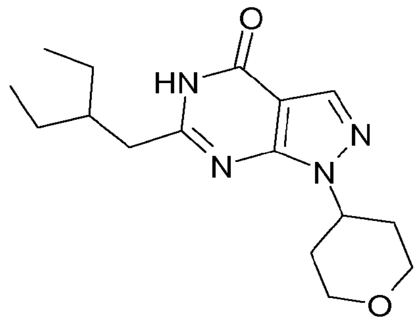
	Structure	pyrazolyl-carbox-amide	Ester	R_t [min]	MS (ESI-APCI, m/z)
Exp. 129 racem. mixture		Exp. 11F	Exp. 5AF	11.56 (Method 2F)	379 $(M+H)^+$
Exp. 130 racem. mixture		Exp. 11F	Exp. 5H	8.38 (Method 1E hydro)	305 $(M+H)^+$
Exp. 131 Enantio-mer A		Exp. 11B	Exp. 5B	9.93 (Method 2F)	331 $(M+H)^+$
Exp. 132 Enantio-mer B		Exp. 11B	Exp. 5C	9.93 (Method 2F)	331 $(M+H)^+$
Exp. 132-1 cis, racem. mixture		Exp. 11IA		9.83 (Method 2F)	291 $(M+H)^+$

	Structure	pyrazolyl-carbox-amide	Ester	R_t [min]	MS (ESI-APCI, m/z)
Exp. 132-2 cis, racem. mixture		Exp. 11IA	Exp. 5AC	10.96 (Method 2F)	317 $(M+H)^+$
Exp. 132-3 Enantio-mer A		Exp. 15A		8.84 (Method 2F)	263 $(M+H)^+$
Exp. 132-4 Enantio-mer B		Exp. 16A		8.96 (Method 2F)	263 $(M+H)^+$
Exp. 132-5 trans, racem. mixture		Exp. 11IB	Exp. 5AC	10.21 (Method 2F)	317 $(M+H)^+$
Exp. 132-6 Enantio-mer B		Exp. 16A		7.15 (Method 1E Hydro)	275 $(M+H)^+$

	Structure	pyrazolyl-carbox-amide	Ester	R_t [min]	MS (ESI-APCI, m/z)
Exp. 132-7 Enantio-mer B		Exp. 16A		5.68 (Method 1E Hydro)	298 $(M+H)^+$
Exp. 132-8 trans, racem. mixture		Exp. 11IB		9.23 (Method 2F)	291 $(M+H)^+$
Exp. 132-9 Enantio-mer A		Exp. 15A		8.83 (Method 2L)	275 $(M+H)^+$

Example 133

6-(2-Ethyl-butyl)-1-(tetrahydro-pyran-4-yl)-1,5-dihydro-pyrazolo[3,4-d]pyrimidin-4-one



Example 11B (0.1 g, 0.48 mmol) was mixed with polyphosphoric acid (1.0 g) and 2-(trifluoromethoxy)phenylacetic acid (248 mg, 1.9 mmol) was added. The mixture was heated to 120°C during 16 hours. Temperature was lowered to 20°C and the pH value was adjusted to 7 by addition of ammonia (30 % solution in water). The aqueous phase was extracted with dichloromethane (2 x 20 mL) and the organic phase was dried over sodium sulphate. The crude mixture was purified by flash chromatography. Eluent: hexane/ethyl acetate 40/60.

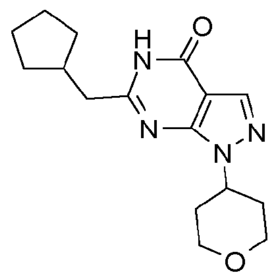
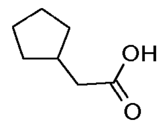
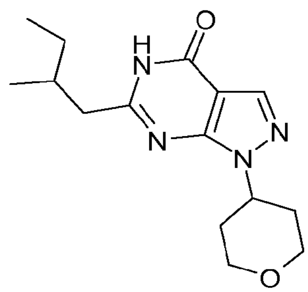
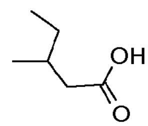
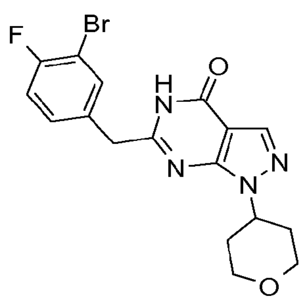
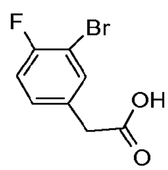
Obtained 23.5 mg (16 %) as a white solid

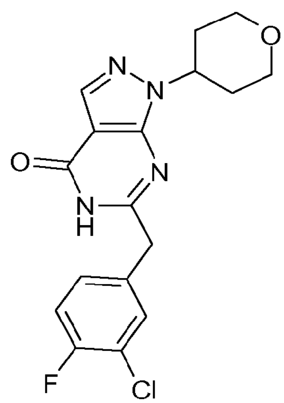
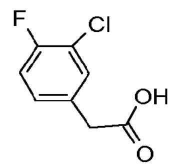
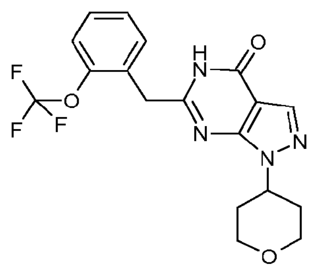
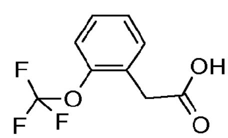
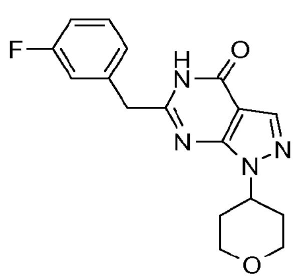
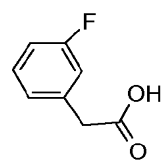
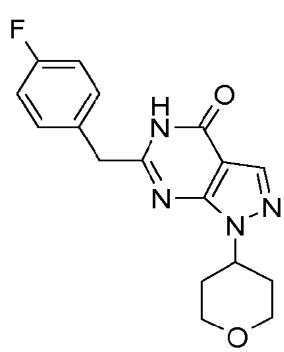
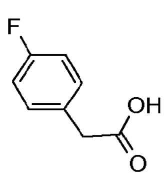
HPLC-MS (1E) R_t: 6.77 min

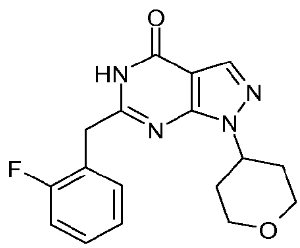
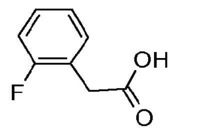
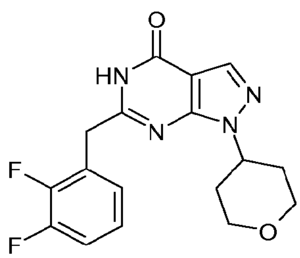
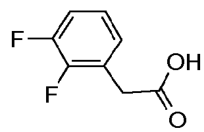
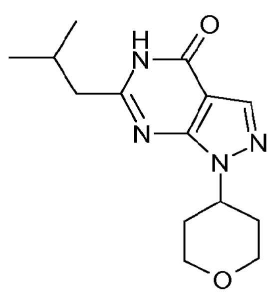
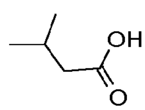
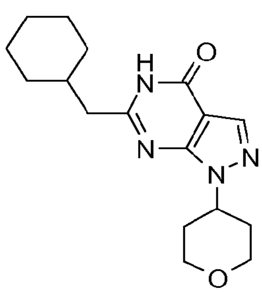
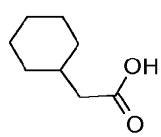
MS (APCI pos): m/z = 305 $(M+H)^+$

The following examples were synthesized in analogy to the preparation of Example 133, using the corresponding carboxylic acids as starting materials:

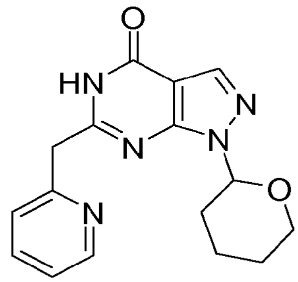
	structure	starting material	R_t [min]	MS (ESI-APCI, m/z)

	structure	starting material	R_t [min]	MS (ESI-APCI, m/z)
Example 134			6.37 (Method 1E)	303 $(M+H)^+$
Example 135 racem. mixture			5.95 (Method 1E)	291 $(M+H)^+$
Example 136			6.57 (Method 1E)	407 $(M+H)^+$

	structure	starting material	R_t [min]	MS (ESI-APCI, m/z)
Example 137			6.48 (Method 1E)	363 $(M+H)^+$
Example 138			6.72 (Method 1E)	395 $(M+H)^+$
Example 139			2.71 (Method Grad_C8_NH_4COOH)	329 $(M+H)^+$
Example 140			2.77 (Method Grad_C8_NH_4COOH)	329 $(M+H)^+$

	structure	starting material	R_t [min]	MS (ESI-APCI, m/z)
Example 141			2.90 (Method Grad_C8_NH_4COOH)	329 $(M+H)^+$
Example 142			3.07 (Method Grad_C8_NH_4COOH)	347 $(M+H)^+$
Example 143			2.71 (Method Grad_C8_NH_4COOH)	277 $(M+H)^+$
Example 144			3.28 (Method Grad_C8_NH_4COOH)	317 $(M+H)^+$

<u>Example 145, racemic mixture</u>

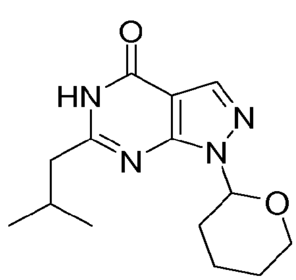


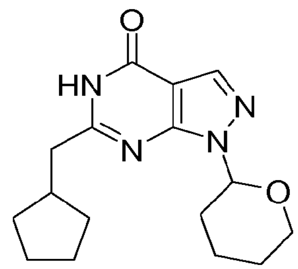
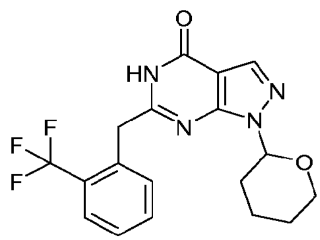
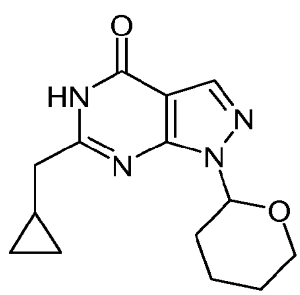
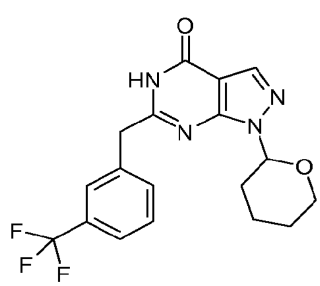
106 mg (0.47 mmol) Example 12V was mixed with 4 mL ethyl acetate and 0.5 mL dimethylformamide, 51 mg (0.61 mmol) 3.4-dihydro-2H-pyran and 88.4 mg (0.51 mmol) p-toluenesulfonic acid were added. The reaction mixture was heated to 60°C and stirred for 2h. After cooling to room temperature ethyl acetate was added and the mixture was washed with saturated sodium hydrogen carbonate and with saturated sodium chloride. The organic layer was evaporated under reduced pressure. The residue was purified by preparative HPLC-MS. 31.5 mg (21.7 %) were obtained.

MS (APCI pos): m/z = 312 $(M+H)^+$

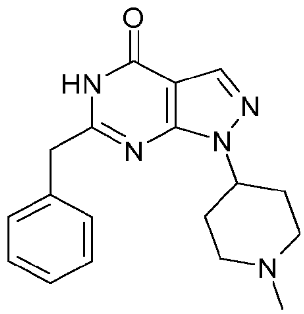
HPLC-MS (Method 2F) R_t: 8.26 min

The following examples were synthesized in analogy to the preparation of Example 145, using the corresponding pyrazolopyrimidinones as starting materials.

	structure	starting material	R_t [min]	MS (ESI-APCI, m/z)
Exp. 146 racem. mixture		Example 12W	9.99 (Method 2F)	277 $(M+H)^+$

	structure	starting material	R_t [min]	MS (ESI-APCI, m/z)
Exp. 147 racem. mixture		Example 12X	10.98 (Method 2F)	303 $(M+H)^+$
Exp. 147-1 racem. mixture		Example 12Y	10.98 (Method 2F)	303 $(M+H)^+$
Example 147-2 racem. mixture		Example 12AA	9.56 (Method 2F)	275 $(M+H)^+$
Example 147-3 racem. mixture		Example 12Z	11.62 (Method 2F)	379 $(M+H)^+$

Example 148

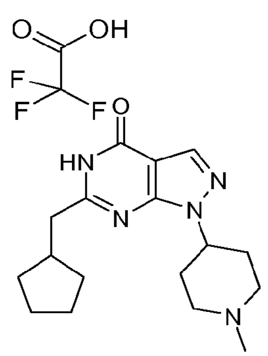


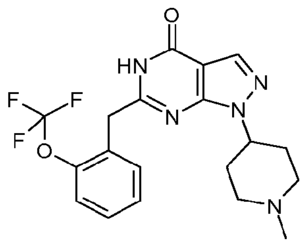
160 mg (470 mmol) of Example 12E was dissolved in 10 mL methanol and 350 mg Raney nickel was added. The reaction mixture was hydrogenated at room temperature for 6h, filtered and the solvent evaporated under reduced pressure. 100 mg (65 %) of the product were obtained.

HPLC-MS (Method 1): R_t: 0.95 min

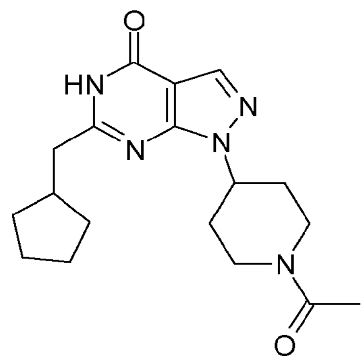
MS (ESI pos): m/z = 324 (M+H)

The following examples were synthesized in analogy to the preparation of Example 148, using the corresponding N-oxides as starting materials.

	structure	starting material	R_t [min]	MS (ESI, m/z)
Exp. 149		Example 12D	0.95 (Method 1)	316 $(M+H)^+$

	structure	starting material	R_t [min]	MS (ESI, m/z)
Exp. 150		Example 12F	1.11 (Method 1)	408 $(M+H)^+$

Example 151

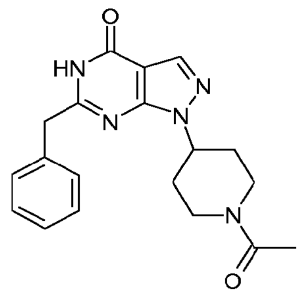
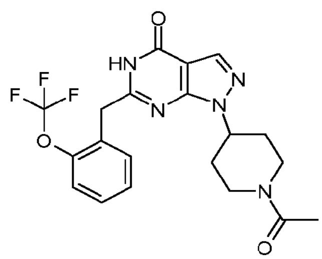
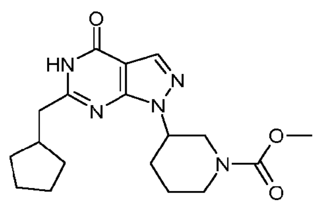
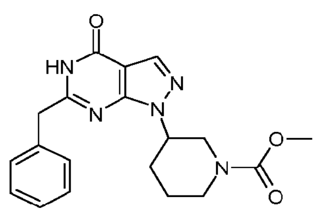


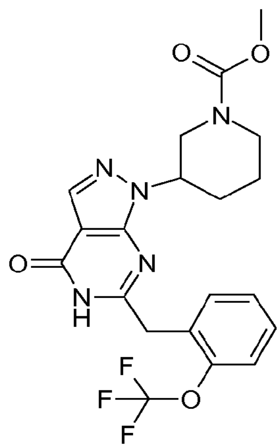
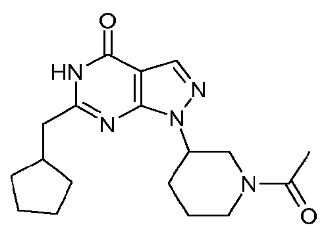
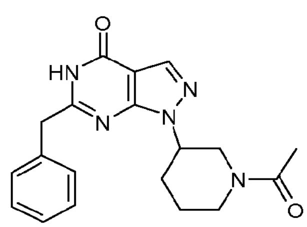
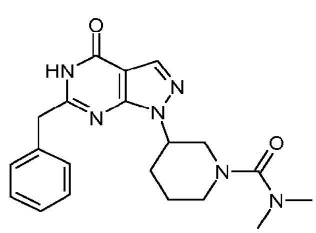
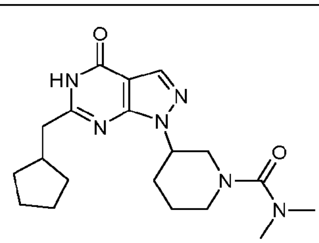
62 mg (150 mmol) of Example 13B were dissolved in 4 mL dichloromethane, 22.5 µL (300 mmol) acetyl chloride and 42 µL (300 mmol) triethylamine were added. The reaction mixture was stirred at room temperature over night. The solvent was removed under reduced pressure. The residue was purified by preparative HPLC (eluent A: water + 0.13 % TFA, eluent B: acetonitrile). 28 mg (55 %) of the product were obtained.

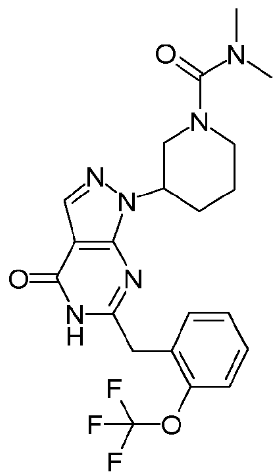
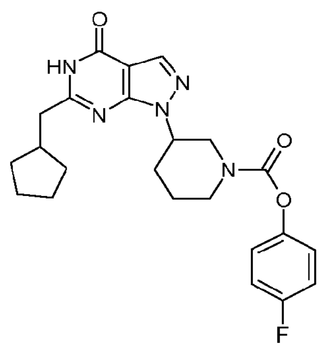
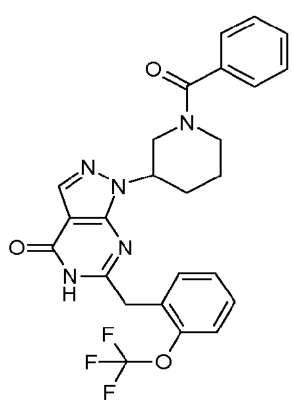
HPLC-MS (Method 1): R_t: 1.18 min

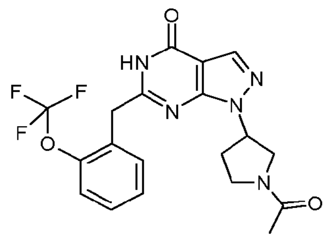
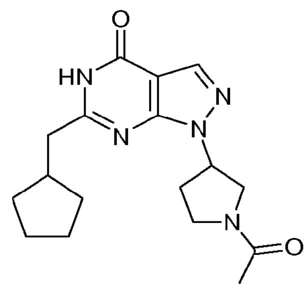
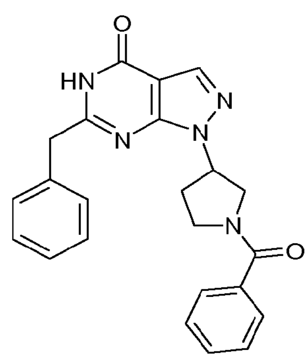
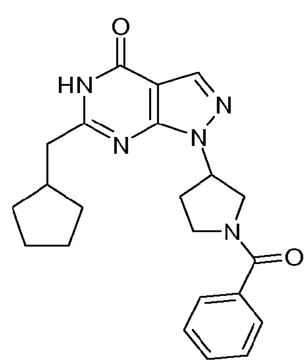
MS (ESI pos): m/z = 344 $(M+H)^+$

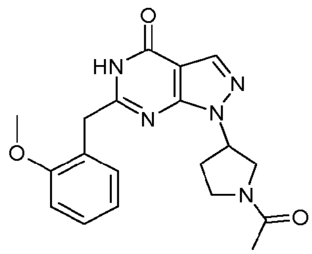
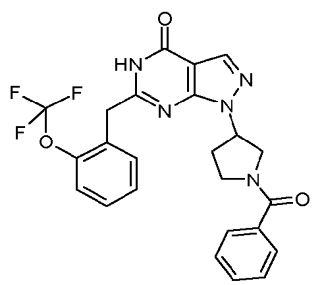
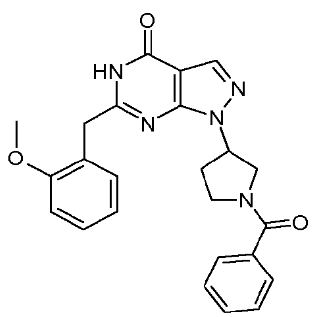
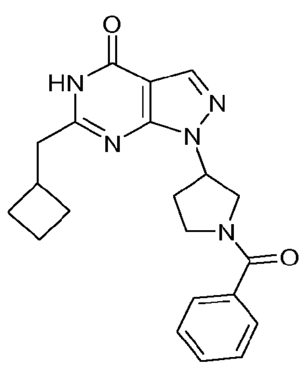
The following examples were synthesized in analogy to the preparation of Example 151, using the corresponding starting materials. It will be evident that as acylating agent not for all compounds acetylchloride has been introduced but other acylating agents like commercially available methoxychloroformate, substituted or unsubstituted aminocarbonylchloride, unsubstituted or substituted phenoxycarbonylchloride, unsubstituted or substituted benzoylchloride were used.

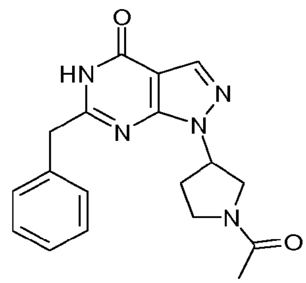
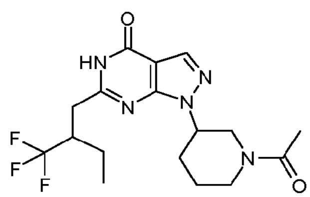
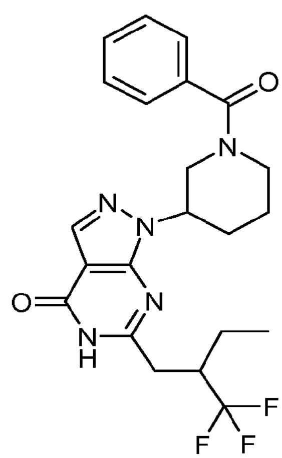
	structure	starting material	R_t [min]	MS (ESI, m/z)
Exp. 152		Example 13K	1.09 (Method 1)	352 $(M+H)^+$
Exp. 153		Example 13L	1.25 (Method 1)	436 $(M+H)^+$
Exp. 154 racem. mixture		Example 13C	1.38 (Method 1)	360 $(M+H)^+$
Exp. 155 racem. mixture		Example 13D	1.30 (Method 1)	368 $(M+H)^+$

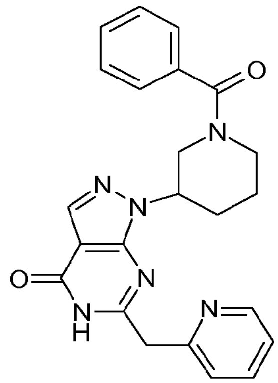
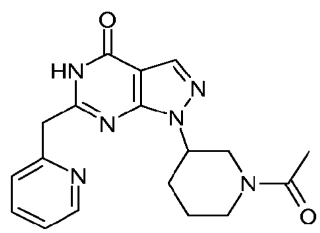
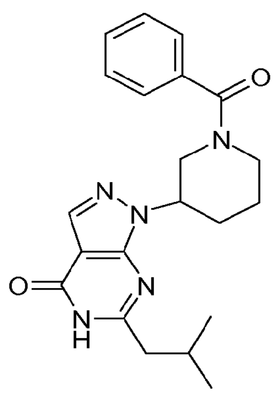
	structure	starting material	R_t [min]	MS (ESI, m/z)
Exp. 156 racem. mixture		Example 13E	1.44 (Method 1)	452 $(M+H)^+$
Exp. 157 racem. mixture		Example 13C	1.20 (Method 1)	344 $(M+H)^+$
Exp. 158 racem. mixture		Example 13D	1.16 (Method 1)	352 $(M+H)^+$
Exp. 159 racem. mixture		Example 13D	1.25 (Method 1)	381 $(M+H)^+$
Exp. 160 racem. mixture		Example 13C	1.30 (Method 1)	373 $(M+H)^+$

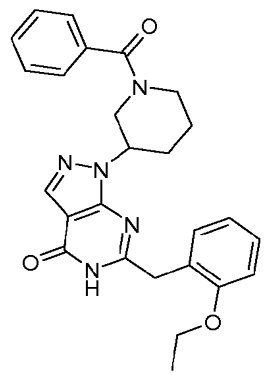
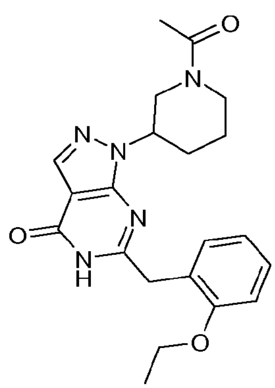
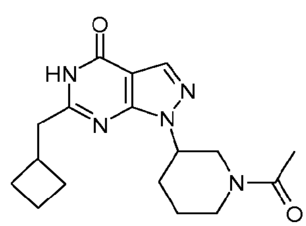
	structure	starting material	R_t [min]	MS (ESI, m/z)
Exp. 161 racem. mixture		Example 13E	1.38 (Method 1)	465 $(M+H)^+$
Exp. 162 racem. mixture		Example 13C	1.62 (Method 1)	440 $(M+H)^+$
Exp. 163 racem. mixture		Example 13E	1.48 (Method 1)	498 $(M+H)^+$

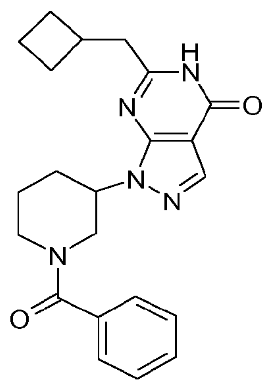
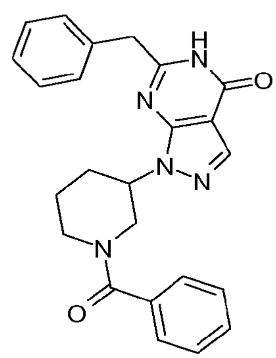
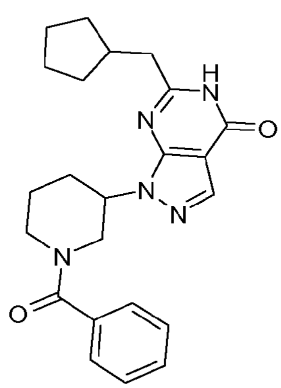
	structure	starting material	R_t [min]	MS (ESI, m/z)
Exp. 164 racem. mixture		Example 13G	1.23 (Method1)	422 $(M+H)^+$
Exp. 165 racem. mixture		Example 13A	1.14 (Method1)	330 $(M+H)^+$
Exp. 166 racem. mixture		Example 13F	1.28 (Method1)	400 $(M+H)^+$
Exp. 167 racem. mixture		Example 13A	1.36 (Method1)	392 $(M+H)^+$

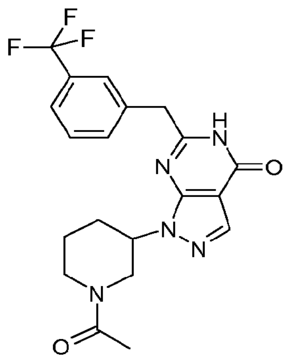
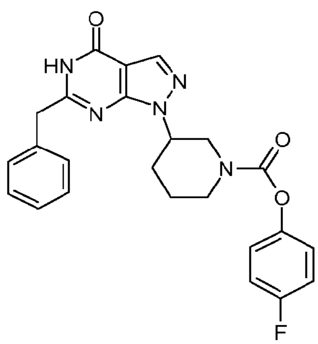
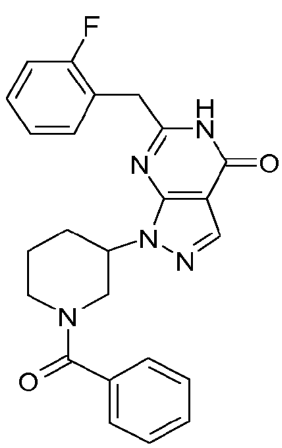
	structure	starting material	R_t [min]	MS (ESI, m/z)
Exp. 168 racem. mixture		Example 13H	1.1 (Method 1)	368 $(M+H)^+$
Exp. 169 racem. mixture		Example 13G	1.44 (Method 1)	484 $(M+H)^+$
Exp. 170 racem. mixture		Example 13H	1.32 (Method 1)	430 $(M+H)^+$
Exp. 171 racem. mixture		Example 13I	1.29 (Method 1)	378 $(M+H)^+$

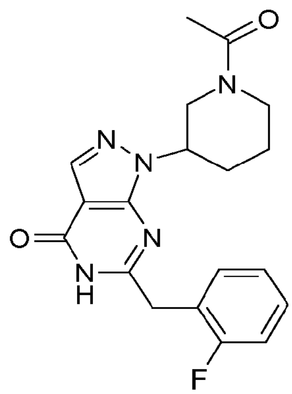
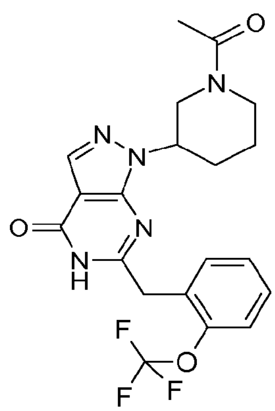
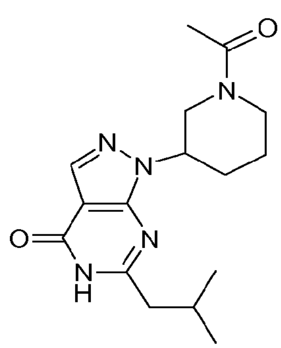
	structure	starting material	R_t [min]	MS (ESI, m/z)
Exp. 172 racem. mixture		Example 13F	1.07 (Method 1)	338 $(M+H)^+$
Exp. 173 mixture of stereoisomers		Example 13M	1.25 (Method 1)	386 $(M+H)^+$
Exp. 174 mixture of stereoisomers		Example 13M	1.44 (Method 1)	448 $(M+H)^+$

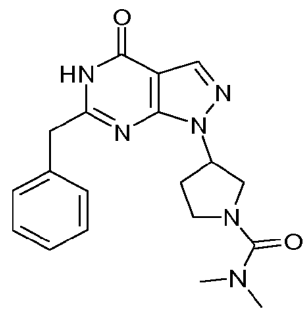
	structure	starting material	R_t [min]	MS (ESI, m/z)
Exp. 175 racem. mixture		Example 13N	1.04 (Method 1)	415 $(M+H)^+$
Exp. 176 racem. mixture		Example 13N	0.84 (Method 1)	353 $(M+H)^+$
Exp. 177 racem. mixture		Example 13O	1.31 (Method 1)	380 $(M+H)^+$

	structure	starting material	R_t [min]	MS (ESI, m/z)
Exp. 178 racem. mixture		Example 13P	1.43 (Method 1)	458 $(M+H)^+$
Exp. 179 racem. mixture		Example 13P	1.24 (Method 1)	396 $(M+H)^+$
Exp. 180 racem. mixture		Example 13Q	1.14 (Method 1)	330 $(M+H)^+$

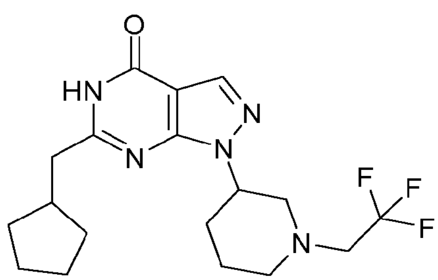
	structure	starting material	R_t [min]	MS (ESI, m/z)
Exp. 181 racem. mixture		Example 13Q	1.34 (Method 1)	392 $(M+H)^+$
Exp. 182 racem. mixture		Example 13D	1.35 (Method 1)	414 $(M+H)^+$
Exp. 183 racem. mixture		Example 13C	1.41 (Method 1)	406 $(M+H)^+$

	structure	starting material	R_t [min]	MS (ESI, m/z)
Exp. 184 racem. mixture		Example 205	1.30 (Method 1)	420 $(M+H)^+$
Exp. 185 racem. mixture		Example 13D	1.53 (Method 1)	448 $(M+H)^+$
Exp. 186 racem. mixture		Example 204	1.35 (Method 1)	432 $(M+H)^+$

	structure	starting material	R_t [min]	MS (ESI, m/z)
Exp. 187 racem. mixture		Example 204	1.15 (Method 1)	370 $(M+H)^+$
Exp. 188 racem. mixture		Example 13E	1.29 (Method 1)	436 $(M+H)^+$
Exp. 189 racem. mixture		Example 13O	1.08 (Method 1)	318 $(M+H)^+$

	structure	starting material	R_t [min]	MS (ESI, m/z)
Exp. 190 racem. mixture		Example 13F	1.18 (Method 1)	367 $(M+H)^+$

Example 191, racemic mixture

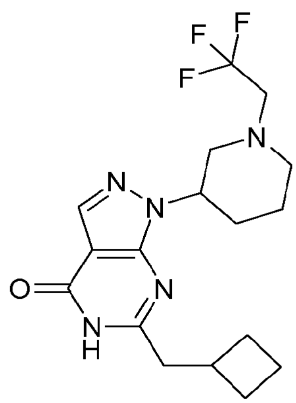
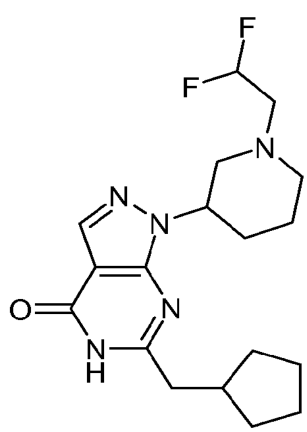


60 mg (0.2 mmol) of Example 13C were dissolved in 5 mL xylene and 57 mg (0.2 mmol) 2,2,2-trifluoroethyl-trichloromethansulfonate were added drop wise. The reaction mixture was heated to 140°C and stirred for 5h. The solvent was removed under reduced pressure. The residue was purified by preparative HPLC (eluent A: water + 0.13 % TFA, eluent B: acetonitrile). 24.8 mg (32 %) of the product were obtained.

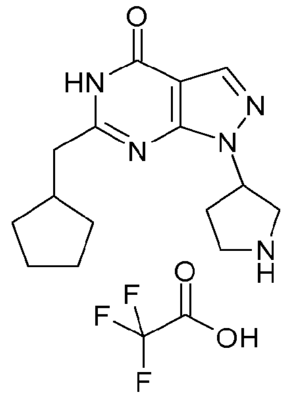
HPLC-MS (Method 1): R_t: 1.45 min

MS (ESI pos): m/z = 384 $(M+H)^+$

The following examples were synthesized in analogy to the preparation of Example 191, using the corresponding starting materials.

	structure	starting material	R_t [min]	MS (ESI, m/z)
Exp. 192 racem. mixture		Example 13Q	1.35 (Method 1)	370 $(M+H)^+$
Exp. 193 racem. mixture		Example 13C	1.07 (Method 1)	366 $(M+H)^+$

Example 194, racemic mixture

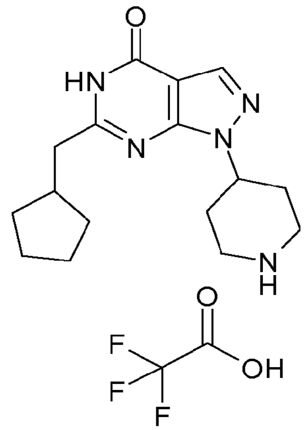


400 mg (1.35 mmol) of Example 11A were dissolved in 8 mL of absolute ethanol, 840 mg (5.4 mmol) of Example 5AC, and 220 mg (5.5 mmol) of sodium hydride (60 % suspension in mineral oil) were added. The reaction mixture was heated to 150°C for 30 min in a microwave oven. After cooling to room temperature, the reaction mixture was acidified with 4N hydrochloride acid. The solvent was removed under reduced pressure. The residue was purified by preparative HPLC (eluent A: water + 0.13 % TFA, eluent B: acetonitrile). 250 mg (46 %) of the product were obtained as a white solid.

HPLC-MS (Method 1): R_t: 0.93 min

MS (ESI pos): m/z = 288 $(M+H)^+$

Example 195



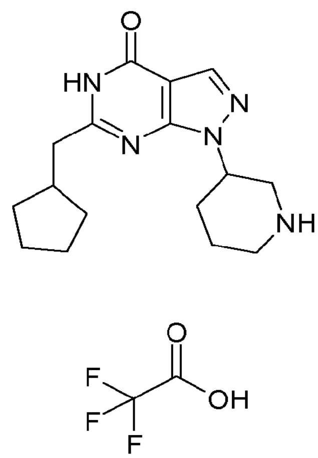
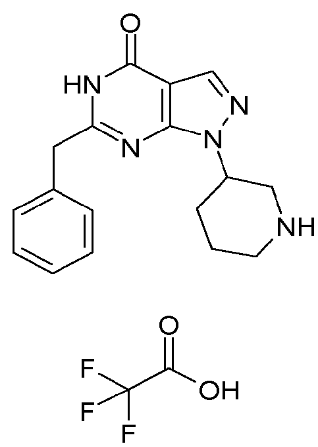
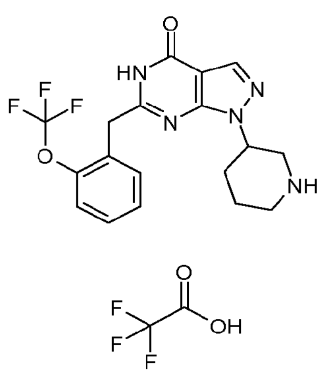
330 mg (0.82 mmol) of Example 12A were dissolved in 3 mL dichloromethane and 1 mL trifluoroacetic acid was added. The reaction mixture was stirred at room temperature over night. The solvent was evaporated under reduced pressure. The residue was purified by preparative HPLC (eluent A: water + 0.13 % TFA, eluent B: acetonitrile). 240 mg (70 %) of the product were obtained.

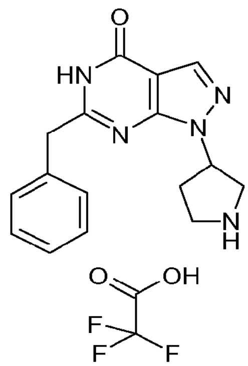
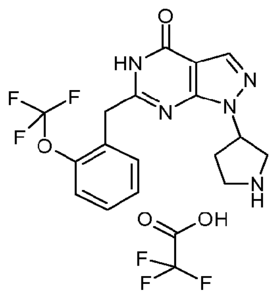
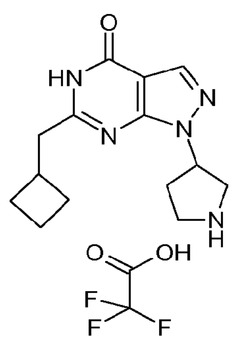
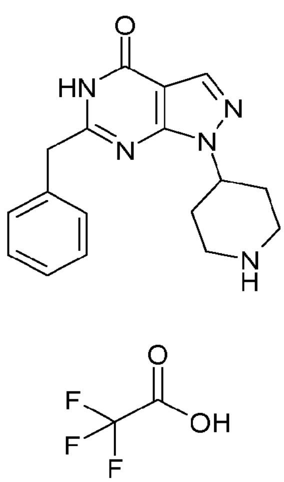
HPLC-MS (Method 1): R_t: 0.96 min

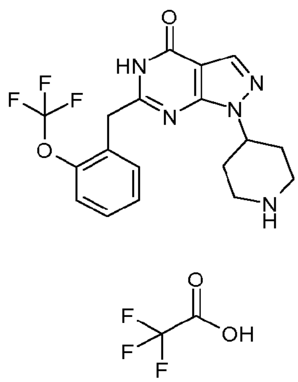
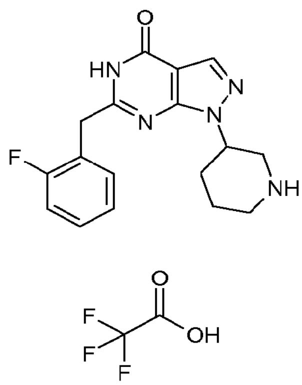
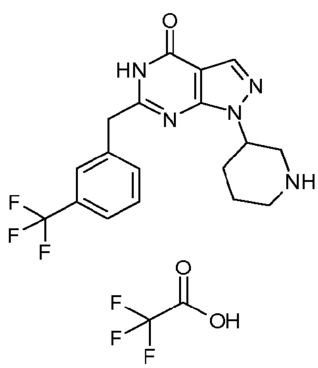
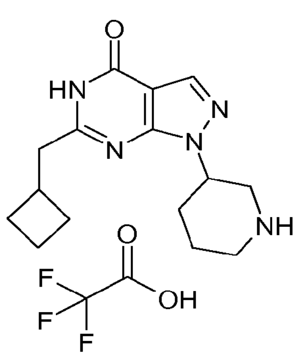
MS (ESI pos): m/z = 302 $(M+H)^+$

The following examples were synthesized in analogy to the preparation of Example 195, using the corresponding Boc-protected amines as starting materials.

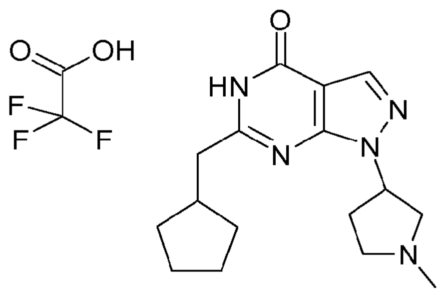
	structure	starting material	R_t [min]	MS (ESI, m/z)

Exp. 196 racem. mixture		Example 12L	1.01 (Method 1)	302 $(M+H)^+$
Exp. 197 racem. mixture		Example 12M	0.93 (Method 1)	310 $(M+H)^+$
Exp. 198 racem. mixture		Example 12N	1.09 (Method 1)	394 $(M+H)^+$

Exp. 199 racem. mixture		Example 12G	0.92 (Method 1)	296 (M+H)$^+$
Exp. 200 racem. mixture		Example 12H	1.08 (Method 1)	380 (M+H)$^+$
Exp. 201 racem. mixture		Example 12J	0.89 (Method 1)	274 (M+H)$^+$
Exp. 202		Example 12B	0.92 (Method1)	310 (M+H)$^+$

Exp. 203		Example 12C	1.07 (Method1)	394 $(M+H)^+$
Exp. 204 racem. mixture		Example 12Q	0.95 (Method 1)	328 $(M+H)^+$
Exp. 205 racem. mixture		Example 12R	1.13 (Method 1)	378 $(M+H)^+$
Exp. 206 racem. mixture		Example 12U	0.94 (Method 1)	288 $(M+H)^+$

Example 207, racemic mixture



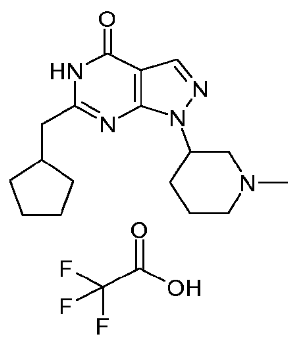
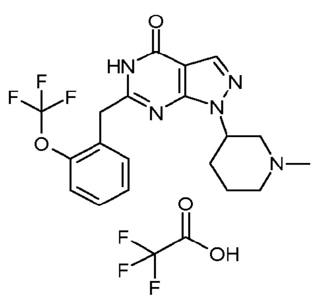
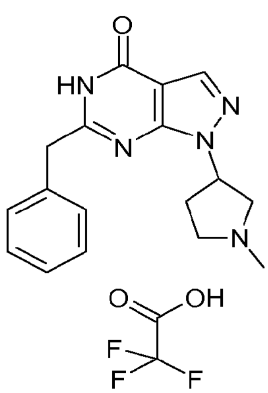
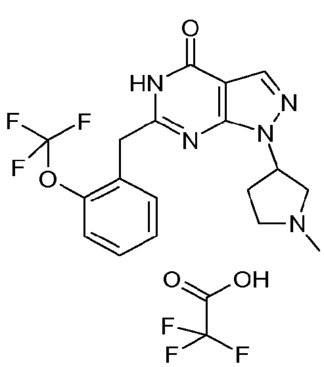
50 mg (120 mmol) of Example 13A were dissolved in 5 mL dichloromethane and 15 mg (500 mmol) of formaldehyde were added. The reaction mixture was stirred at room temperature for 1h. 15 µL (260 mmol) acetic acid and 35 mg (160 mmol) sodiumtriacetoxyborohydride were added. The reaction mixture was stirred 2h at room temperature. The solvent was removed under reduced pressure. The residue was purified by preparative HPLC (eluent A: water + 0.13 % TFA, eluent B: acetonitrile). 34 mg (65 %) of the product were obtained.

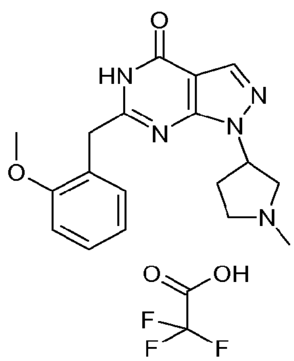
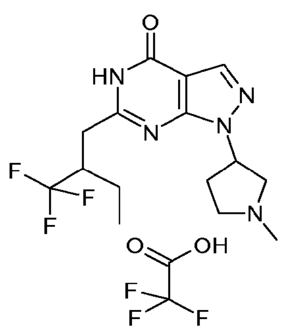
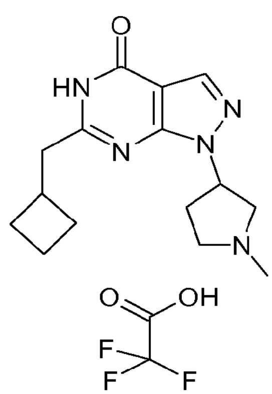
HPLC-MS (Method 1): R_t: 0.99 min

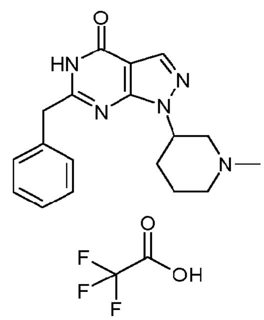
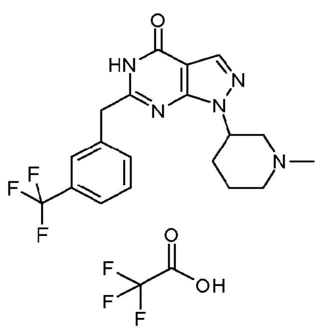
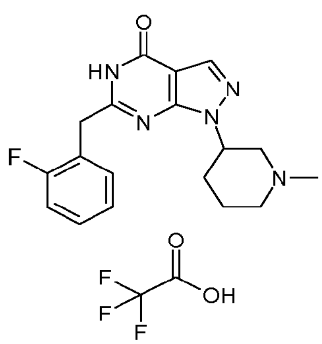
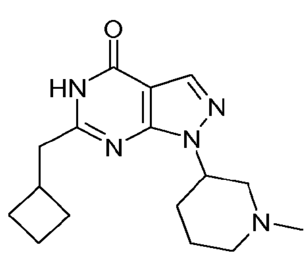
MS (ESI pos): m/z = 302 $(M+H)^+$

The following examples were synthesized in analogy to the preparation of Example 207 using the corresponding amines as starting materials

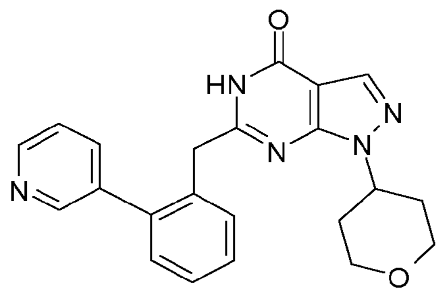
	structure	starting material	R_t [min]	MS (ESI, m/z)

	structure	starting material	R_t [min]	MS (ESI, m/z)
Exp. 208 racem. mixture		Example 13C	1.02 (Method 1)	316 $(M+H)^+$
Exp. 209 racem. mixture		Example 13E	1.13 (Method 1)	408 $(M+H)^+$
Exp. 210 racem. mixture		Example 13F	0.93 (Method 1)	310 $(M+H)^+$
Exp. 211 racem. mixture		Example 13G	1.11 (Method 1)	394 $(M+H)^+$

	structure	starting material	R_t [min]	MS (ESI, m/z)
Exp. 212 racem. mixture		Example 13H	0.98 (Method 1)	340 $(M+H)^+$
Exp. 213 mixture of stereoisomers		Example 13J	1.02 (Method 1)	344 $(M+H)^+$
Exp. 214 racem. mixture		Example 13I	0.91 (Method 1)	288 $(M+H)^+$

	structure	starting material	R_t [min]	MS (ESI, m/z)
Exp. 215 racem. mixture		Example 13D	0.97 (Method 1)	324 $(M+H)^+$
Exp. 216 racem. mixture		Example 205	1.16 (Method 1)	392 $(M+H)^+$
Exp. 217 racem. mixture		Example 204	0.98 (Method 1)	342 $(M+H)^+$
Exp. 218 racem. mixture		Example 13Q	0.95 (Method 1)	302 $(M+H)^+$

Example 219



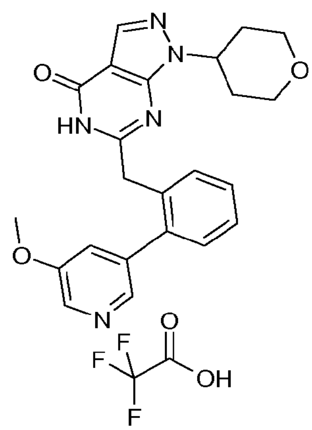
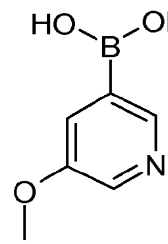
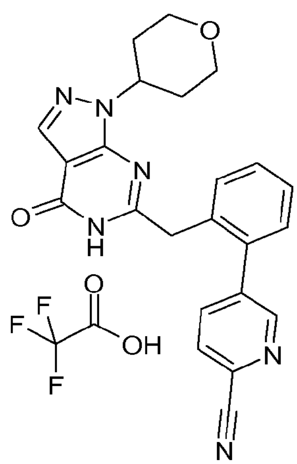
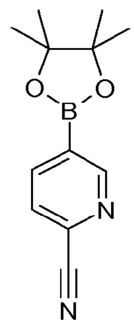
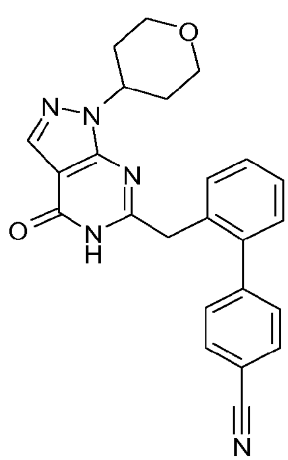
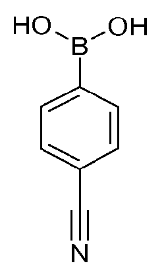
Under a argon atmosphere 100 mg (0.26 mmol) of example 5, 95 mg (0.77 mmol) pyridine-3-boronic acid, 310 µL (2.41 mmol) aqueous sodium carbonate solution (2 M), 5 mL dioxane and 20 mg (0.02 mmol) tetrakis-(triphenylphosphine)palladium(0) were combined. The reaction mixture was heated to 140°C for 35 min in a microwave oven. After cooling to room temperature the reaction mixture was filtered over celite. The filtrate was evaporated under reduced pressure. The residue was purified by preparative HPLC. 82 mg (83 %) of the product were obtained.

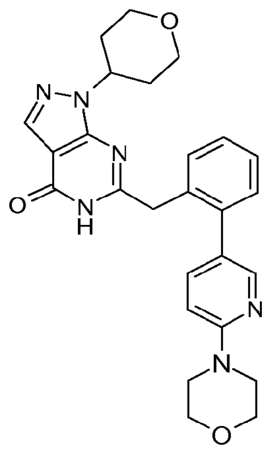
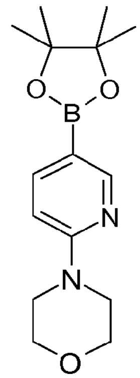
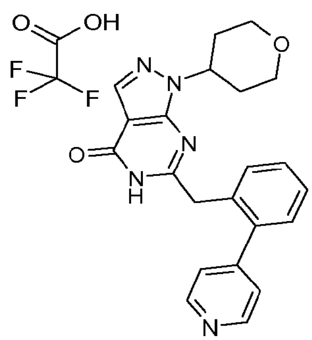
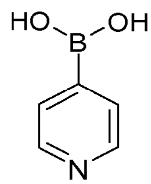
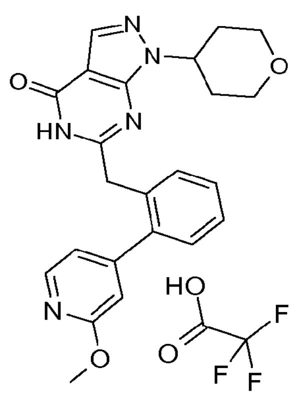
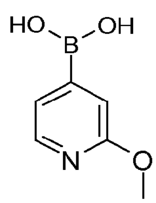
HPLC-MS (Method 1): R_t: 1.00 min

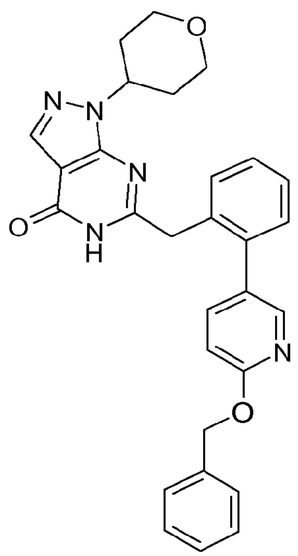
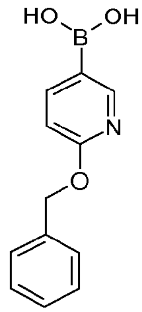
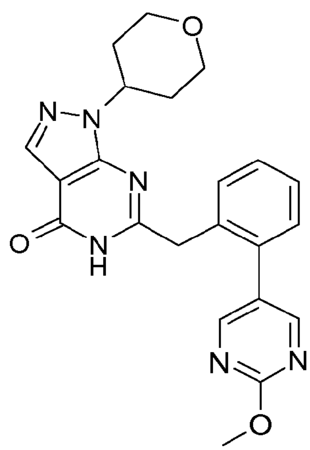
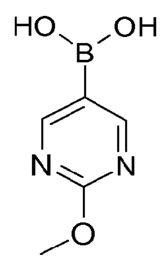
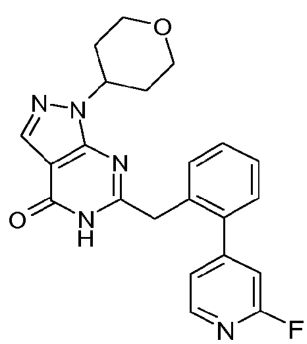
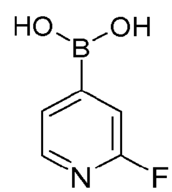
MS (ESI pos): m/z = 388 $(M+H)^+$

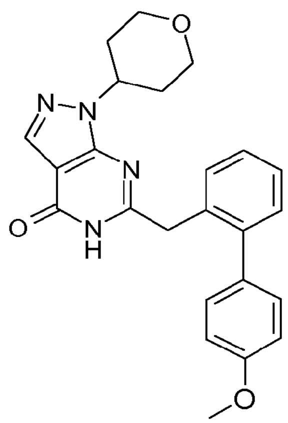
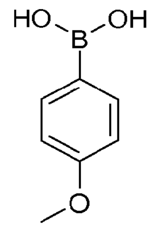
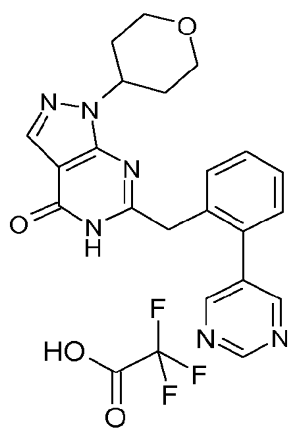
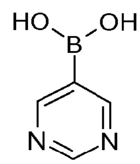
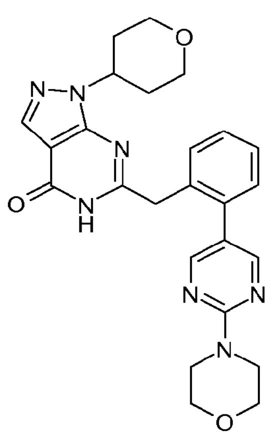
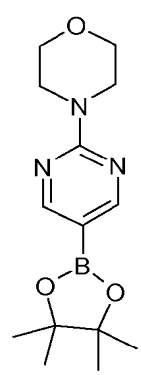
The following examples were synthesized in analogy to the preparation of example 219 using the corresponding boronic acids as starting materials.

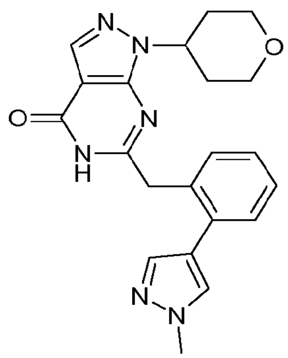
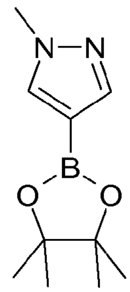
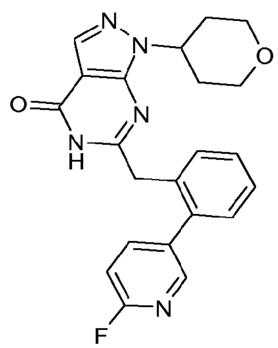
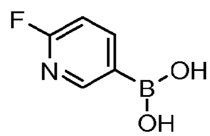
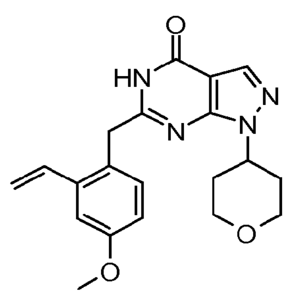
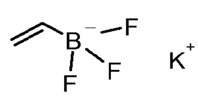
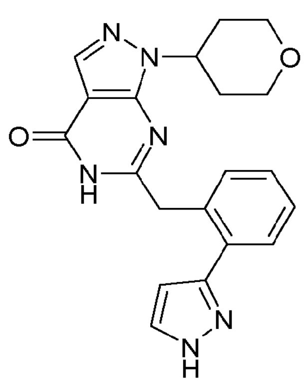
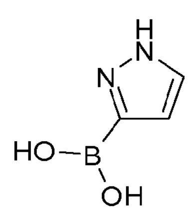
	structure	starting material	R_t [min]	MS (ESI, m/z)

	structure	starting material	R_t [min]	MS (ESI, m/z)
Example 220			1.01 (Method 1)	418 $(M+H)^+$
Example 221			1.24 (Method 1)	413 $(M+H)^+$
Example 222			1.34 (Method 1)	412 $(M+H)^+$

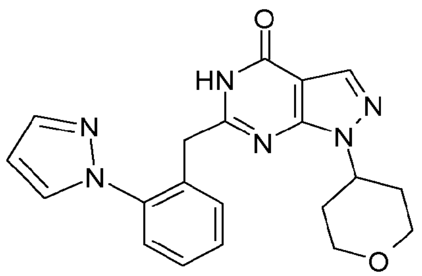
	structure	starting material	R_t [min]	MS (ESI, m/z)
Example 223			1.03 (Method 1)	473 $(M+H)^+$
Example 224			0.96 (Method 1)	388 $(M+H)^+$
Example 225			1.18 (Method 1)	418 $(M+H)^+$

	structure	starting material	R_t [min]	MS (ESI, m/z)
Example 226			1.57 (Method 1)	494 $(M+H)^+$
Example 227			1.19 (Method 1)	419 $(M+H)^+$
Example 228			1.26 (Method 1)	406 $(M+H)^+$

	structure	starting material	R_t [min]	MS (ESI, m/z)
Example 229			1.40 (Method 1)	417 $(M+H)^+$
Example 230			1.06 (Method 1)	389 $(M+H)^+$
Example 230-1			1.24 (Method 1)	474 $(M+H)^+$

	structure	starting material	R_t [min]	MS (ESI, m/z)
Example 230-2			1.16 (Method 1)	391 $(M+H)^+$
Example 230-3			1.25 (Method 1)	404 $(M+H)^+$
230-4			1.28 (Method 1)	367 $(M+H)^+$
230-5			1.27 (Method 1)	377 $(M+H)^+$

Example 231

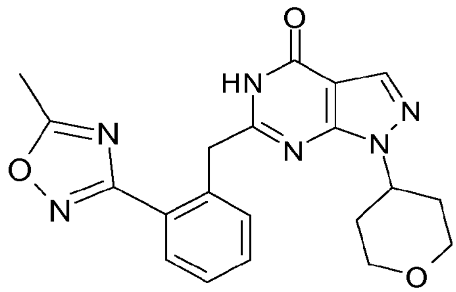


A vial was charged under inert atmosphere with Example 5 (175 mg, 0.45 mmol), pyrazole (306 mg, 4.49 mmol), copper iodide (85 mg, 0.45 mmol) and cesium carbonate (439 mg, 1.35 mmol). Dimethylformamide (5 ml), previously degassed, was then added, followed by N-N'-dimethylethylenediamine (47.87 µl; 0.45 mmol). The reaction mixture was heated to 120 °C for three hours.The suspension was then filtered over a Celite pad; Celite was washed with DMF. The volume of the organic phase was reduced under reduced pressure and, afterwards, ammonium chloride saturated solution was added, followed by ethyl acetate. The phases were separated and the organic phase was washed with brine and then dried. The crude product was purified by SPE cartridge and the product obtained was further purified by SPE Stratosphere "PL-THIOL MP" to completely remove copper salts. The solid obtained was triturated with diethyl ether. 15.5 mg of the desired compound were obtained (yield = 9.2%).

HPLC-MS (Method 1E hydro): R_t: 7.80 min

MS (APCI pos): m/z = 377 $(M+H)^+$

Example 232



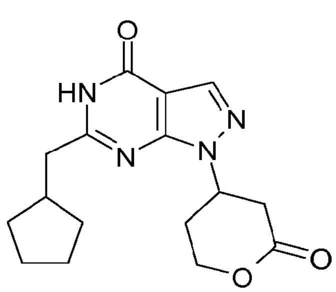
Example 53 (100 mg, 0.298 mmol) and hydroxylamine (0.073 ml, 1.19 mmol) were mixed together in absolute ethanol (4 ml) in a 50 ml flask. The reaction mixture was refluxed for 3 hours before being worked up. The solvent was then removed under reduced pressure to obtain 120 mg (content 70%, 0.228 mmol) of N-Hydroxy-2-[4-oxo-1-(tetrahydro-pyran-4-yl)-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidin-6-ylmethyl]-benzamidine as solid that was used as such in the next step.

N-Hydroxy-2-[4-oxo-1-(tetrahydro-pyran-4-yl)-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidin-6-ylmethyl]-benzamidine (120 mg, content 70%; 0.228 mmol) was suspended in trimethylorthoacetate (5 ml) and acetic acid was added afterwards (1 ml); the mixture was heated to 100 °C for one hour. The mixture was cooled at room temperature and the precipitation of a solid was observed. The filtrate was evaporated under reduced pressure; the crude product was purified by flash chromatography. The product was then triturated with diethyl ether. 24 mg of the desired compound were obtained (yield 26.6%).

HPLC/MS (Method 1E hydro)

MS (APCI pos): m/z = 393 $(M+H)^+$

Example 233



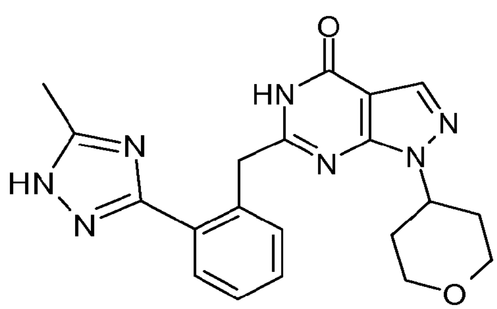
Example 12X (250 mg, 1.14 mmol) was dissolved in 20 ml of hot methanol. Alumina (neutral) was added and the solvent was then removed to give a white powder which was transferred into a 2 ml Wheaton vial; 5,6-Dihydro-2H-pyran-2-oxo was added followed by DMFe (1ml) and the vial was closed tightly. The suspension was heated to 80°C with orbital shaking during 4 days. The reaction was then filtered and the alumina was washed with methanol, ethyl acetate and dicholoromethane; the organic solutions were combined and solvents removed under reduced pressure. The crude product was purified by flash chromatography.

Eluent: (gradient starting with n-hexane/ethyl acetate 9/1 to ethyl acetate (100%) followed by ethyl acetate/methanol 99/1 to 94/6). 70 mg of the desired compound were obtained as solid (19.3 %).

HPLC-MS (Method 2F): R_t: 9.06 min

MS (ESI pos): m/z = 317 $(M+H)^+$

<u>Example 234</u>



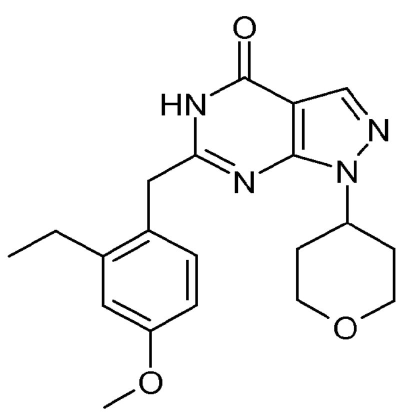
Example 53 (160 mg, content 80% ,0.38 mmol) and hydrazine hydrate (0.186 ml, 3.81 mmol) were mixed together in absolute ethanol (4 ml) in a 25 ml flask. The reaction mixture was refluxed for 6 hours before being worked up. The solvent was removed under reduced pressure to obtain 200 mg (content 70%, 0.38 mmol) of the desired material used as such in the next step. The material (200mg, 70% content, 0.38 mmol) was suspended in trimethylorthoacetate (6 ml). Acetic acid is added (0.6 ml) and the solution was heated to 80°C for 30 minutes. Trimethylortoacetate and

acetic acid were removed under reduced pressure and the crude product was partitioned between water and dichloromethane. The organic phase is dried and the crude product purified by flash chromatography. (gradient: starting with dichloromethane/methanol 98/2 and finishing with dichloromethane/methanol 90/10). The product was further purified by trituration with diethyl ether. 8 mg of the desired compound were obtained (4%).

HPLC-MS (Method 1E hydro): R_t: 6.82 min

MS (APCI pos): m/z = 392 $(M+H)^+$

Example 235

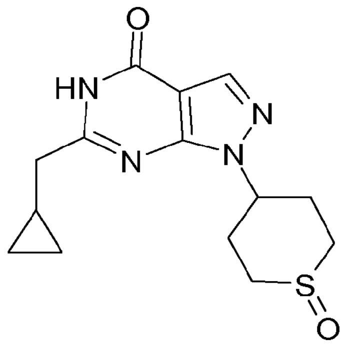


22 mg (0.06 mmol) of example 230-4 in 3 ml methanol were hydrogenated over Pd/C (10 %) under atmospheric pressure. The catalyst was removed. The solvent was evaporated and the residue chromatographed by HPLC (eluent A: water + 0.13 % TFA, eluent B: acetonitrile) to yield 15.7 mg (71 %) of the product.

HPLC-MS (Method 1): R_t: 1.35 min

MS (ESI pos): m/z = 369 $(M+H)^+$

Example 236

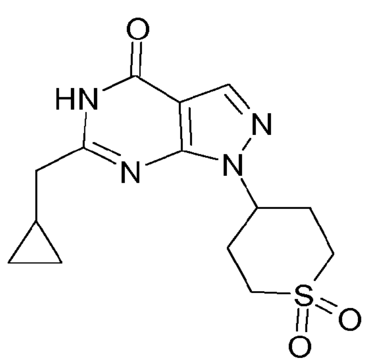


100 mg (73 %, 0.251 mmol) of example 40-5 were dissolved in 2 ml acetic acid and 30 µL (0.35 mmol) hydrogen peroxide solution in water (35 %) were added. The mixture was stirred for 3 h and acetonitrile/water was added. The mixture was chromatographed by HPLC (eluent A: water + 0.13 % TFA, eluent B: acetonitrile) to yield 50.3 mg (65 %) of the product.

HPLC-MS (Method 1): R_t: 0.88 min

MS (ESI pos): m/z = 307 $(M+H)^+$

Example 237



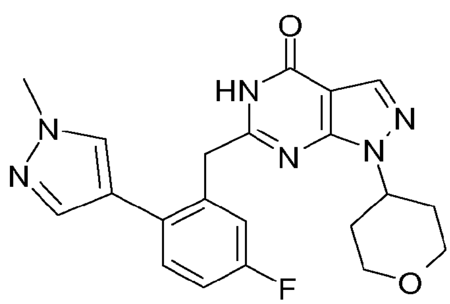
100 mg (73 %, 0.251 mmol) of example 40-5 were dissolved in 2 ml acetic acid and 200 µL (2.33 mmol) hydrogen peroxide solution in water (35 %) were added. The mixture was stirred for 3 days and acetonitrile/water was added. The mixture was

chromatographed by HPLC (eluent A: water + 0.13 % TFA, eluent B: acetonitrile) to yield 21.5 mg (27 %) of the product.

HPLC-MS (Method 1): R_t: 0.93 min

MS (ESI pos): m/z = 323 $(M+H)^+$

Example 239

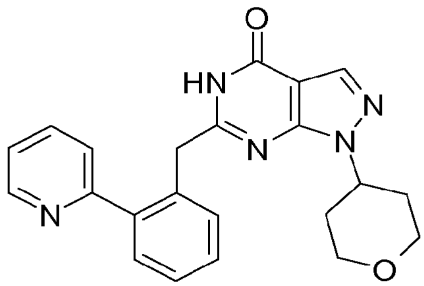


Under a nitrogen atmosphere 50.0 mg (0.12 mmol) of example 40-10 and 51 mg (0.25 mmol) 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole were dissolved in 2 mL DMF. 156 mg (0.74 mmol) potassium phosphate, 0.78 mg (2.45 µmmol) tris(dibenzylideneacetone)dipalladium and 2.85 mg tri(tert-butylphosphonium)tetrafluoroborate were added. The reaction mixture was heated to 150°C for 30 min in a microwave oven. The mixture was evaporated under reduced pressure. The residue was purified by preparative HPLC. 29 mg (58 %) of the product were obtained.

HPLC-MS (Method 1): R_t: 1.23 min

MS (ESI pos): m/z = 409 $(M+H)^+$

Example 240



Step A:

1.00 g (6.33 mmol) 2-bromo-pyridine and 1.53 mL (6.46 mmol) triisopropyl borate were dissolved in 10 mL THF under nitrogen. The mixture was cooled to -30°C. 6.76 mL (10.8 mmol) n-buthyllithium were added dropwise. After stirring for 1.5 h the mixture was allowed to warm to room temperature within 1 h. The precipitate was filtered off and dried to yield 0.84 g of solid material.

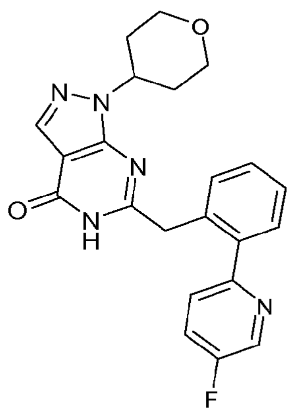
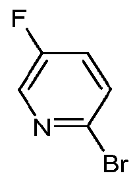
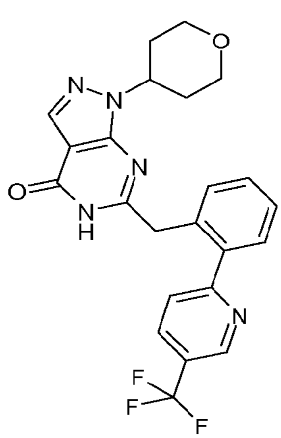
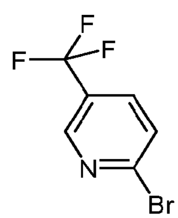
Step B:

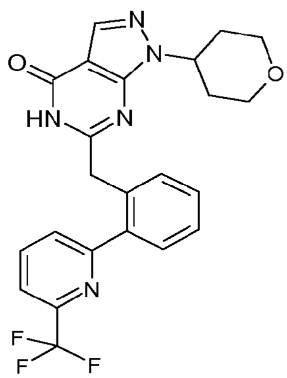
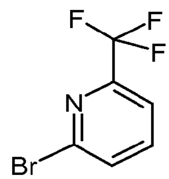
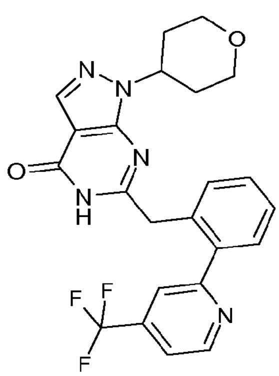
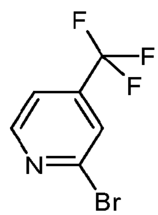
To 100 mg (0.26 mmol) of example 5 and 213 mg of the product obtained in step A, 3 mL DMF, 436 mg (2.05 mmol) of potassium phosphate and 26.7 mg (0.02 mmol) tetrakis-(triphenylphosphine)-palladium(0) were added. The reaction mixture was heated to 145°C for 90 min in a microwave oven. The mixture was evaporated under reduced pressure. The residue was taken up in dichloromethane and washed with water and brine. The organic layer was separated, dried and evaporated under reduced pressure. The residue was purified by preparative HPLC (eluent A: water + 0.1% conc. ammonia, eluent B: methanol). The resulting material was further purified by a three step procedure: (1) conversion into the corresponding hydrochloride salt by addition of dichloromethane followed by hydrochloric acid (6 M in isopropanol) and subsequent evaporation of the volatiles under reduced pressure; (2) trituration with acetonitrile and subsequent removal of the solvent by filtration; and (3) liberation of the free base by addition of dichloromethane and extraction with an aqueous solution of potassium carbonate followed by phase separation and removal of the solvent from the organic layer under reduced pressure. 9.1 mg (9.1 %) of the product were obtained.

HPLC-MS (Method 4): R_t = 2.57 min

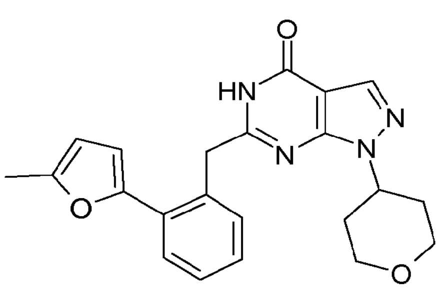
MS (ESI pos): m/z = 388 $(M+H)^+$

The following example was synthesized in analogy to the preparation of example 240, using the corresponding starting materials.

	structure	starting material: bromo-pyridine	R_t	MS (ESI pos, m/z)
Example 241			3.04 min (Method 4)	406 $(M+H)^+$
Example 242			3.29 min (Method 4)	456 $(M+H)^+$

	structure	starting material: bromo-pyridine	R_t	MS (ESI pos, m/z)
Example 243			3.10 min (Method 4)	456 $(M+H)^+$
Example 244			3.37 min (Method 4)	456 $(M+H)^+$

Example 245

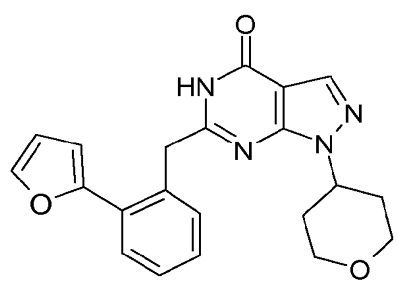


A microwave vial was charged with Example 5 (100 mg, 0.257 mmol), 5-Methylfuran-2-boronic acid (161.75 mg, 1.285 mmol), Tetrakis(triphenylphosphine)palladium(0) (118.84 mg, 0.104 mmol) in Dioxane (1mL); afterwards 1.02 mL (2.056 mmol) of a 2M aqueous solution of Na_2CO_3 were added. The reaction mixture was heated to 130°C for 4 hours in a microwave oven. Cooling to 20°C was followed by acidification with HCl 37% until acidic pH and then extraction with dichloromethane (2x 2mL). The organic layer was dried over Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure. The remaining residue was purified by flash chromatography on SiO_2 using cyclohexane/ethyl acetate mixture of increasing polarity (from 100% cyclohexane to 100% ethyl acetate) as eluent. The product obtained was further purified by preparative TLC (ethyl acetate/cyclohexane 80/20 as eluent). The solid was freeze-dried with a water/acetonitrile 1:1 mixture yielding the title compound as a white solid (23 mg, 22.9%).

HPLC-MS (Method 1E hydro): R_t: 8.93 min

MS (APCI pos): m/z = 391 $(M+H)^+$

Example 246



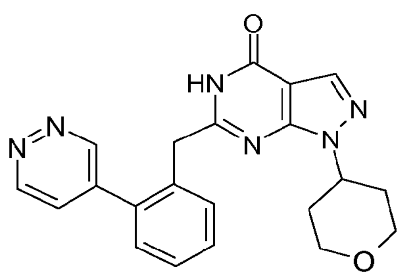
A microwave vial was charged with Example 5 (90 mg, 0.231 mmol), 2-Furanboronic acid (77.74 mg, 0.694 mmol), Tetrakis(triphenylphosphine)palladium(0) (40.74 mg, 0.035 mmol) in Dioxane (1mL); afterwards 0.46 mL (0.925 mmol) of a 2M aqueous solution of Na_2CO_3 were added. The reaction mixture was heated to 130°C for 80 min in a microwave oven. Cooling to 20°C was followed by dilution with water and acidification with HCl 10% aqueous solution then extraction with dichloromethane (2x

2mL). The organic layer was dried over Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure. The remaining residue was purified preparative HPLC (eluent A: water + NH_4COOH 5 mM, eluent B: acetonitrile). After freeze-drying the title compound was obtained as a white solid (28 mg, 32.2%).

HPLC-MS (Method 1E hydro): R_t: 8.42 min

MS (APCI pos): m/z = 377 $(M+H)^+$

Example 247

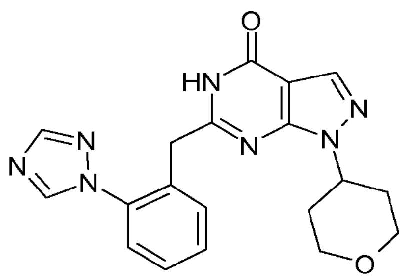


A vial was charged under inert atmosphere with Example 5 (100 mg, 0.514 mmol) and 4-(tributylstannyl)pyridazine (227.6 mg, 0.617 mmol) in previously degassed toluene (7 mL), afterwards Tetrakis(triphenylphosphine)palladium(0) (59.37 mg, 0.051 mmol) and copper iodide (9.79 mg, 0.051mmol) were added. The reaction mixture was heated to 120°C for 2 hours in a microwave oven. The reaction mixture was diluted with saturated NH_4Cl water solution and extracted with dichloromethane. The organic layer was dried over Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography on SiO_2 using dichloromethane/methanol 98/2 as eluent. The solid obtained was further purified by preparative HPLC (eluent A: water + NH_4COOH 5 mM, eluent B: acetonitrile). The title compound was obtained as a white solid (22 mg, 11 %).

HPLC-MS (Method 1E hydro): R_t: 6.33 min

MS (APCI pos): m/z = 389 $(M+H)^+$

Example 248

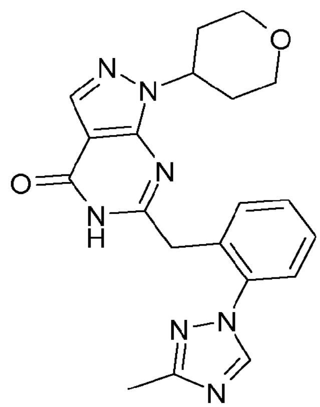
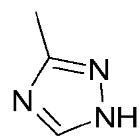
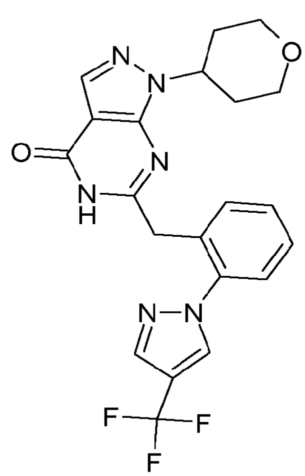
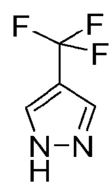


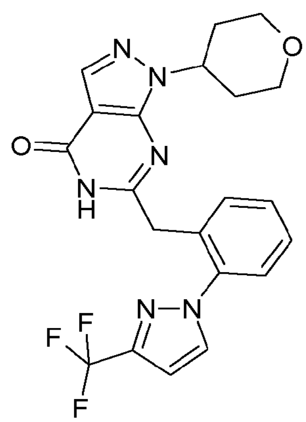
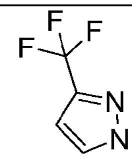
A round bottom flask was charged under inert atmosphere with copper iodide (97.86 mg, 0.514 mmol), cesium carbonate (502.23 mg, 1.541 mmol), Example 5 (200 mg, 0.514 mmol), 1,2,4-triazole (384.56 mg, 5.138 mmol) and then dimethylformamide (12 mL), previously degassed, followed by N-N'-dimethylethylenediamine (109.4 µL, 1.028 mmol). The reaction mixture was heated to 120 °C for 3 hours. After cooling the reaction mixture was filtered through a Celite pad that was rinsed with dimethylformamide then saturated NH_4Cl aqueous solution was added and extracted with ethyl acetate. The organic phase was washed with saturated NH_4Cl aqueous solution, brine then dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was purified by preparative HPLC (eluent A: water + NH_4COOH 5 mM, eluent B: acetonitrile). The title compound was obtained as a solid (7.2 mg, 3.7 %).

HPLC-MS (Method 1E Hydro): R_t: 6.37 min

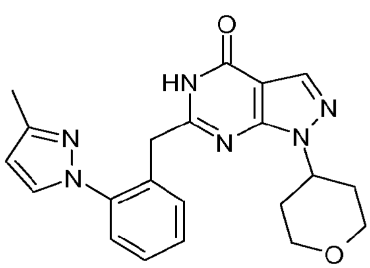
MS (APCI pos): m/z = 378 $(M+H)^+$

The following examples were synthesized in analogy to the preparation of Example 248, using the corresponding bromides and heterocycles as starting materials:

	Structure	starting material: heterocycle	R_t [min]	MS (APCI pos, m/z)
Example 249			6.52 (Method 1E hydro)	392 $(M+H)^+$
Example 250			8.75 Method 1E hydro	445 $(M+H)^+$

	Structure	starting material: heterocycle	R_t [min]	MS (APCI pos, m/z)
Example 251			8.63 Method 1E hydro	445 $(M+H)^+$

Example 252



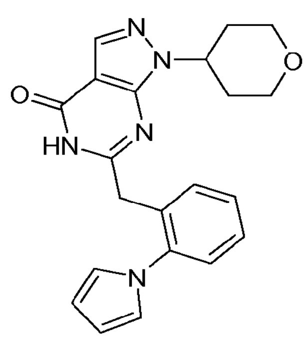
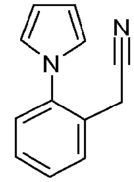
79.89 mg (0.380 mmol) of Example 11B were dissolved in absolute ethanol (2 mL) and 76 mg (1.9 mmol) of sodium hydride (60% suspension in mineral oil) were added. The mixture was stirred for 10 minutes before the addition of 300 mg (1.521 mmol) of [2-(3-Methyl-pyrazol-1-yl)-phenyl]-acetonitrile (Example 20A). Then the reaction mixture was heated to 140°C for 40 minutes in a microwave oven. Cooling to 20°C was followed by evaporation of the solvent under reduced pressure. The residue was dissolved in 10% citric acid aqueous solution (2 mL) then extracted with dichloromethane (2 x 2 mL). The organic phase was dried over Na_2SO_4, filtered and

the solvent was removed under reduced pressure. The residue was purified by preparative HPLC (eluent A: water + 0.05% TFA, eluent B: acetonitrile). The solid obtained was triturated with diisopropyl ether to give the title compound as a solid (50.8 mg, 34.2%).

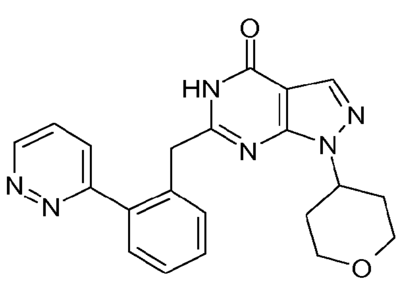
HPLC-MS (Method 2M): R_t = 8.41 min

MS (APCI pos): m/z = 391 $(M+H)^+$

The following examples were synthesized in analogy to the preparation of Example 252, using the corresponding ester or nitrile as starting materials:

	Structure	pyrazolyl-carboxamide	nitrile	R_t [min]	MS (ESI pos, m/z)
Example 253		Example 11B	 Example 21A	10.09 Method 2F	376 $(M+H)^+$

Example 254

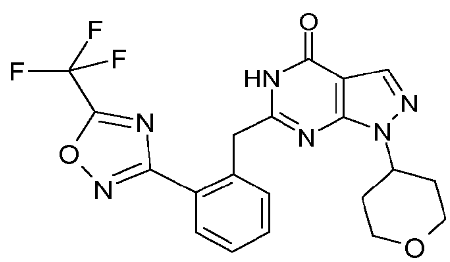


A microwave vial was charged with Example 19A (50 mg, 0.115 mmol), 3-bromopyridazine (15 mg, 0.094 mmol) and 1,2-Dimethoxyethane (2.5 mL). The mixture was degassed and then Tetrakis(triphenylphosphine)palladium(0) (16.35 mg, 0.014 mmol) and 165.11 µL (0.33 mmol) of a 2M aqueous solution of Na_2CO_3 were added. The reaction mixture was heated to 120°C for 1 hour in a microwave oven. After cooling to 20°C the reaction mixture was diluted with saturated NH_4Cl aqueous solution and extracted with dichloromethane, dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on SiO_2 using Dichloromethane/Methanol 98/2 as eluent. The title compound was obtained as a solid (12 mg, 32.8%).

HPLC-MS (Method 1E Hydro): R_t: 7.12 min

MS (APCI pos): m/z = 389 $(M+H)^+$

Example 255



Example 53 (200 mg, 0.596 mmol) and hydroxylamine 50% in water (146.18 µL, 2.385 mmol) were mixed together in absolute ethanol (6 mL). The reaction mixture was refluxed for 5 hours. The solvent was then removed under reduced pressure to obtain 229 mg (0.621 mmol) of N-Hydroxy-2-[4-oxo-1-8tetrahydro-pyran-4-yl)-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidin-6-ylmethyl]-benzamidine as a yellow solid that was used as such in the next step.

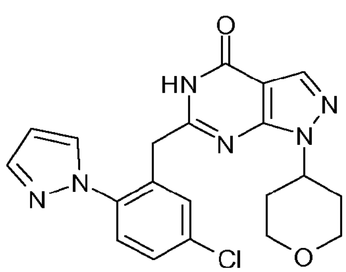
N-Hydroxy-2-[4-oxo-1-8tetrahydro-pyran-4-yl)-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidin-6-ylmethyl]-benzamidine (225mg, 0.611 mmol) was suspended in dry dichloromethane (4.5 mL), N,N-Diisopropylethylamine (0.79 mL, 4.616 mmol) was added and the reaction mixture was cooled to 0 °C before the addition of Trifluoroacetic anhydride (0.402 mL, 2.89 mmol). The mixture was stirred at 0 °C for

5 hours before being diluted with dichloromethane and washed with water and brine. The organic phase was dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The remaining residue was purified by flash chromatography on SiO_2 using dichloromethane/methanol mixture of increasing polarity (from 100% Dichloromethane to 99/1 Dichloromethane/Methanol) as eluant. The product was obtained as a light yellow solid (55 mg, 20.2%).

HPLC-MS (Method 1E Hydro): R_t: 9.22 min

MS (APCI pos): m/z = 447 $(M+H)^+$

Example 256

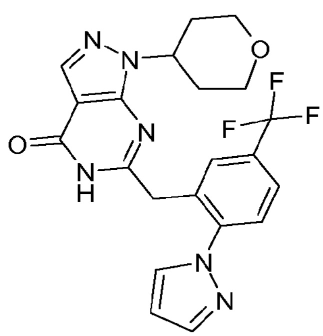
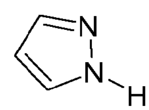
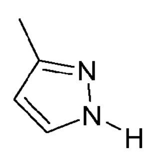


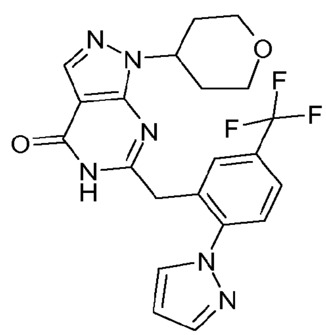
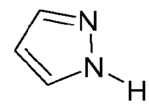
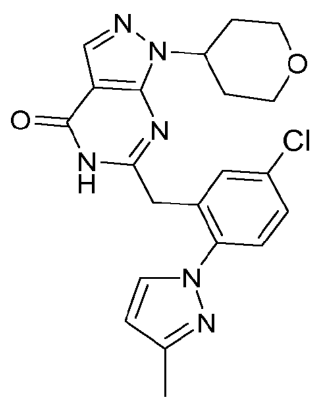
A microwave reactor vial was charged under inert atmosphere with copper(I)oxide (5.1 mg, 0.04 mmol), cesium carbonate (154 mg, 0.47 mmol), 2-hydroxy-benzaldehyde oxime (9.7 mg, 0.07 mmol), Example 40-8 (100 mg, 0.24 mmol) and pyrazole (32.1 mg, 0.47 mmol). Acetonitrile (5 mL), previously degassed, was added. The reaction mixture was heated to 80°C for 2 hours using a microwave oven. After cooling the reaction mixture was diluted with dichloromethane and filtered through a Celite pad. The solvent was removed under reduced pressure. The crude product was purified by preparative HPLC (A: water + 0.05% TFA, eluent B: methanol). The resulting material was further purified by a three step procedure: (1) conversion into the corresponding hydrochloride salt by addition of ethyl acetate followed by hydrochloric acid (6 M in isopropanol) and subsequent evaporation of the volatiles under reduced pressure; (2) trituration with ethyl acetate and subsequent removal of the solvent by filtration; and (3) liberation of the free base by addition of ethyl acetate and extraction with an aqueous solution of potassium carbonate followed by phase

separation and removal of the solvent from the organic layer under reduced pressure. 30 mg (31 %) of the product were obtained.

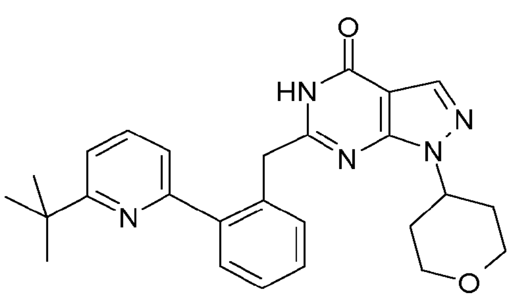
HPLC-MS (Method 6): R_t = 1.45 min
MS (ESI pos): m/z = 411/413 $(M+H)^+$ (Cl)

The following example was synthesized in analogy to the preparation of Example 256, using the corresponding bromide and heterocycle as starting materials:

	Structure	starting material: bromide	starting material: heterocycle	R_t [min]	MS (ESI pos, m/z)
Example 257		Example 40-9		1.50 (Method 6)	445 $(M+H)^+$
Example 258		Example 40-8		1.46 (Method 7)	425/427 $(M+H)^+$ (Cl)

	Structure	starting material: bromide	starting material: heterocycle	R_t [min]	MS (ESI pos, m/z)
Example 257		Example 40-9		1.50 (Method 6)	445 $(M+H)^+$
					

Example 259

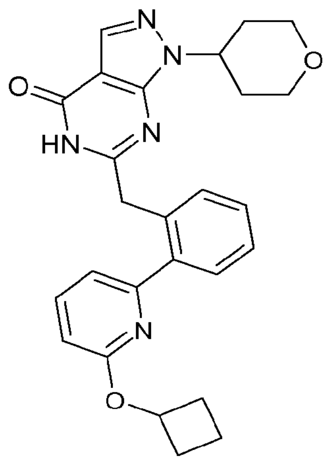
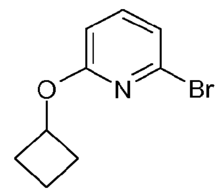
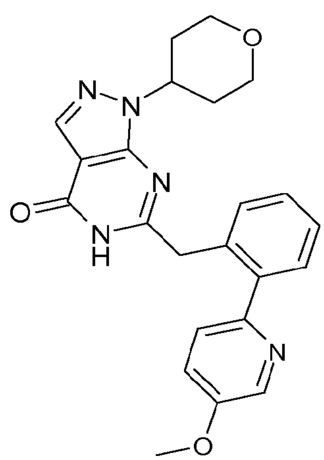
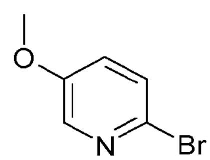


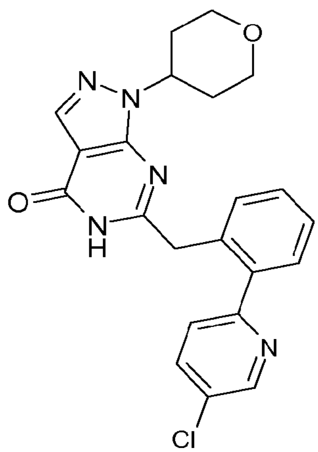
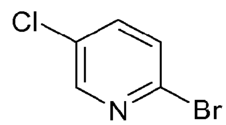
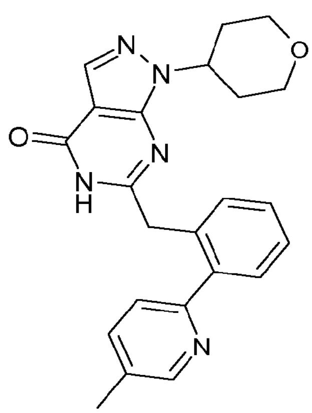
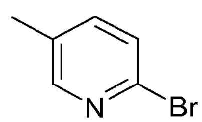
A microwave vial was charged with Example 19A (70 mg, 0.16 mmol), 2-bromo-6-tert-butyl-pyridine (69 mg, 0.32 mmol) and DMF (2.0 mL). The mixture was degassed then Tetrakis(triphenylphosphine)palladium(0) (9.2 mg, 0.01 mmol) and potassium acetate (55.1 mg, 0.56 mmol) were added. The reaction mixture was heated to 145°C for 45 min in a microwave oven. After cooling to 20°C the solvent was removed under reduced pressure. The crude product was purified by preparative HPLC (A: water + 0.05% TFA, eluent B: methanol). The resulting material was further purified by a two step procedure: (1) conversion into the corresponding hydrochloride salt by addition of dichloromethane followed by hydrochloric acid (6 M in isopropanol) and subsequent evaporation of the volatiles under reduced pressure; and (2) trituration with ethyl acetate and subsequent removal of the solvent by filtration. 47 mg (61 %) of the product were obtained as the hydrochloride salt.

HPLC-MS (Method 7): R_t = 1.42 min
MS (ESI pos): m/z = 444 $(M+H)^+$

The following example was synthesized in analogy to the preparation of example 259, using the corresponding bromopyridines as starting materials:

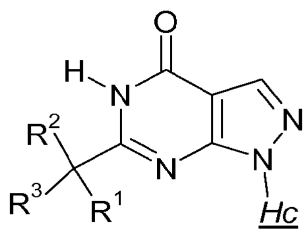
	structure	starting material: bromo-pyridine	R_t	MS (ESI pos, m/z)

	structure	starting material: bromo-pyridine	R_t	MS (ESI pos, m/z)
Example 260			1.62 min (Method 7)	458 $(M+H)^+$
Example 261			1.38 min (Method 7)	418 $(M+H)^+$

	structure	starting material: bromo-pyridine	R_t	MS (ESI pos, m/z)
Example 262			1.53 min (Method 7)	422 $(M+H)^+$
Example 263			1.22 min (Method 7)	402 $(M+H)^+$

Claims

1. A compound according to general formula (I)



(I),

with

Hc being tetrahydropyranyl-, preferably 4-tetrahydropyranyl,

whereby one or more carbon ring atom(s) thereof optionally may be substituted by one or by two substituents independently selected from the group of fluorine, NC-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, C_{1-6}-alkyl-, C_{1-6}-alkyl-O- and up to one carbon ring atom may be substituted with oxo;

$\mathbf{R^1}$ being the group

V—W—*

wherein

W is selected from the group of phenyl or heteroaryl;

V is selected from the group of phenyl or heteroaryl;

V preferably is attached at the 2 position of **W**, whereby the 1 position of **W** is the attachment point of **W** to the CR^2R^3 group in formula (I);

-* is the binding point by which **W** is attached to the CR^2R^3 group in formula (I);

wherein **W** and **V** independently of each other optionally may be substituted by one or more substituents selected from the group of fluorine, chlorine, bromine, C_{1-6}-alkyl-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, F_3C-O-, HF_2C-O-, C_{3-7}-heterocycloalkyl-, H-O-C_{1-6}-alkyl-, C_{1-6}-alkyl-O-C_{1-6}-alkyl-, C_{3-7}-cycloalkyl-O-C_{1-6}-alkyl-, C_{3-7}-cycloalkyl-C_{1-3}-alkyl-O-C_{1-6}-alkyl-, phenyl-O-C_{1-6}-alkyl-, benzyl-O-C_{1-6}-alkyl-, H-O-, C_{1-6}-alkyl-O-, C_{3-7}-cycloalkyl-O-, C_{3-7}-cycloalkyl-C_{1-3}-alkyl-O-, phenyl-O-, benzyl-O-, N-morpholinyl, and NC-, preferably by a substituent selected from the group of fluorine, chlorine, bromine, C_{1-6}-alkyl-, F_3C-, F_3C-CH_2-, F_3C-O-, HF_2C-O-, C_{3-7}-heterocycloalkyl-, C_{1-6}-alkyl-O-, C_{3-6}-cycloalkyl-O-, C_{3-6}-cycloalkyl-CH_2-O-, aryl-CH_2-O- and NC-;

$\mathbf{R^2}$ being selected from the group of H-, fluorine, F_3C-, HF_2C-, FH_2C-, and C_{1-3}-alkyl-, preferably $\mathbf{R^2}$ being H;

$\mathbf{R^3}$ being selected from the group of H-, fluorine, F_3C-, HF_2C-, FH_2C-, and C_{1-3}-alkyl-, preferably $\mathbf{R^3}$ being H.

2. A compound according to claim 1, wherein

Hc being tetrahydropyranyl-, preferably 4-tetrahydropyranyl,

whereby one or more carbon ring atom(s) thereof optionally may be substituted by one or two substituents independently selected from the group of fluorine, NC-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, C_{1-6}-alkyl-, C_{1-6}-alkyl-O- and up to one carbon ring atom may be substituted with oxo;

$\mathbf{R^1}$ being the group

V—W—*

wherein

W is selected from the group of phenyl or a heteroaryl, said heteroaryl being selected from the group of oxadiazolyl, triazolyl, pyrazolyl, furanyl, pyridyl, pyrimidyl and pyridazinyl,

V is selected from the group of phenyl or heteroaryl, said heteroaryl being selected from the group of oxadiazolyl, triazolyl, pyrazolyl, pyrrolyl, furanyl, pyridyl, pyrimidyl and pyridazinyl,

V preferably is attached at the 2 position of **W**, whereby the 1 position of **W** is the attachment point of **W** to the CR^2R^3 group in formula (I);

wherein **W** and **V** independently of each other optionally may be substituted by one or more substituents selected from the group of fluorine, chlorine, bromine, C_{1-6}-alkyl-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, F_3C-O-, HF_2C-O-, C_{3-7}-heterocycloalkyl-, H-O-C_{1-6}-alkyl-, C_{1-6}-alkyl-O-C_{1-6}-alkyl-, C_{3-7}-cycloalkyl-O-C_{1-6}-alkyl-, C_{3-7}-cycloalkyl-C_{1-3}-alkyl-O-C_{1-6}-alkyl-, phenyl-O-C_{1-6}-alkyl-, benzyl-O-C_{1-6}-alkyl-, H-O-, C_{1-6}-alkyl-O-, C_{3-7}-cycloalkyl-O-, C_{3-7}-cycloalkyl-C_{1-3}-alkyl-O-, phenyl-O-, benzyl-O-, N-morpholinyl, and NC-, preferably by a substituent selected from the group of fluorine, chlorine, bromine, C_{1-6}-alkyl-, F_3C-, F_3C-CH_2-, F_3C-O-, HF_2C-O-, C_{3-7}-heterocycloalkyl-, C_{1-6}-alkyl-O-, C_{3-6}-cycloalkyl-O-, C_{3-6}-cycloalkyl-CH_2-O-, aryl-CH_2-O- and NC-;

$\mathbf{R^2}$ being selected from the group of H-, fluorine, F_3C-, HF_2C-, FH_2C-, and C_{1-3}-alkyl-, preferably $\mathbf{R^2}$ being H;

R^3 being selected from the group of H-, fluorine, F_3C-, HF_2C-, FH_2C-, and C_{1-3}-alkyl-, preferably **R**^{3} being H.

3. A compound according to claim 1, wherein
Hc being tetrahydropyranyl-,

whereby one or more carbon ring atom(s) thereof optionally may be substituted by one or two substituents independently selected from the group of fluorine, NC-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, C_{1-6}-alkyl-, C_{1-6}-alkyl-O- and up to one carbon ring atom may be substituted with oxo;

R^1 being the group

V—W—*

wherein

W is selected from the group of phenyl or a heteroaryl, said heteroaryl being selected from the group of pyridyl, pyrimidyl and pyridazinyl,

V is selected from the group of phenyl or heteroaryl, said heteroaryl being selected from the group of oxadiazolyl, triazolyl, pyrazolyl, pyrrolyl, furanyl, pyridyl, pyrimidyl and pyridazinyl,

V preferably is attached at the 2 position of **W**, whereby the 1 position of **W** is the attachment point of **W** to the CR^2R^3 group in formula (I);

wherein **W** and **V** independently of each other optionally may be substituted by one or more substituents selected from the group of fluorine, chlorine, bromine, C_{1-6}-alkyl-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, F_3C-O-, HF_2C-O-, C_{3-7}-heterocycloalkyl-, H-O-C_{1-6}-alkyl-, C_{1-6}-alkyl-O-C_{1-6}-alkyl-, C_{3-7}-cycloalkyl-O-C_{1-6}-alkyl-, C_{3-7}-cycloalkyl-C_{1-3}-alkyl-O-C_{1-6}-alkyl-, phenyl-O-C_{1-6}-alkyl-, benzyl-O-C_{1-6}-alkyl-, H-O-, C_{1-6}-alkyl-O-, C_{3-7}-cycloalkyl-O-, C_{3-7}-cycloalkyl-C_{1-3}-alkyl-O-, phenyl-O-, benzyl-O-, N-morpholinyl, and NC-, preferably by a substituent selected from the group of fluorine, chlorine, bromine, C_{1-6}-alkyl-, F_3C-, F_3C-CH_2-, F_3C-O-, HF_2C-O-, C_{3-7}-heterocycloalkyl-, C_{1-6}-alkyl-O-, C_{3-6}-cycloalkyl-O-, C_{3-6}-cycloalkyl-CH_2-O-, aryl-CH_2-O- and NC-;

$\mathbf{R^2}$ being selected from the group of H-, fluorine, F_3C-, HF_2C-, FH_2C-, and C_{1-3}-alkyl-, preferably $\mathbf{R^2}$ being H;

$\mathbf{R^3}$ being selected from the group of H-, fluorine, F_3C-, HF_2C-, FH_2C-, and C_{1-3}-alkyl-, preferably $\mathbf{R^3}$ being H.

4. A compound according to claim 1, wherein
Hc being tetrahydropyranyl-,

whereby one or more carbon ring atom(s) thereof optionally may be substituted by one or two substituents independently selected from the group of fluorine, NC-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, C_{1-6}-alkyl-, C_{1-6}-alkyl-O- and up to one carbon ring atom may be substituted with oxo;

$\mathbf{R^1}$ being the group

V—W—*

wherein

W is selected from the group of phenyl or pyridinyl,

V is selected from the group of phenyl or heteroaryl, said heteroaryl being selected from the group of oxadiazolyl, triazolyl, pyrazolyl, furanyl, pyridyl, pyrimidyl and pyridazinyl,

V preferably is attached at the 2 position of **W**, whereby the 1 position of **W** is the attachment point of **W** to the CR^2R^3 group in formula (I);

wherein **W** and **V** independently of each other optionally may be substituted by one or more substituents selected from the group of fluorine, chlorine, bromine, C_{1-6}-alkyl-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, F_3C-O-, HF_2C-O-, C_{3-7}-heterocycloalkyl-, H-O-C_{1-6}-alkyl-, C_{1-6}-alkyl-O-C_{1-6}-alkyl-, C_{3-7}-cycloalkyl-O-C_{1-6}-alkyl-, C_{3-7}-cycloalkyl-C_{1-3}-alkyl-O-C_{1-6}-alkyl-, phenyl-O-C_{1-6}-alkyl-, benzyl-O-C_{1-6}-alkyl-, H-O-, C_{1-6}-alkyl-O-, C_{3-7}-cycloalkyl-O-, C_{3-7}-cycloalkyl-C_{1-3}-alkyl-O-, phenyl-O-, benzyl-O-, N-morpholinyl, and NC-, preferably by a substituent selected from the group of fluorine, chlorine, bromine, C_{1-6}-alkyl-, F_3C-, F_3C-CH_2-, F_3C-O-, HF_2C-O-, C_{3-7}-heterocycloalkyl-, C_{1-6}-alkyl-O-, C_{3-6}-cycloalkyl-O-, C_{3-6}-cycloalkyl-CH_2-O-, aryl-CH_2-O- and NC-,

wherein more preferably **W** and **V** independently of each other optionally may be substituted by one or more substituents selected from the group of fluorine, chlorine, H_3C-, F_3C-, CH_3O-, N-morpholinyl, and NC-, more preferably selected from the group of fluorine, H_3C-, F_3C-, CH_3O- and NC-;

$\mathbf{R^2}$ being selected from the group of H-, fluorine, F_3C-, HF_2C-, FH_2C-, and C_{1-3}-alkyl-, preferably $\mathbf{R^2}$ being H;

$\mathbf{R^3}$ being selected from the group of H-, fluorine, F_3C-, HF_2C-, FH_2C-, and C_{1-3}-alkyl-, preferably $\mathbf{R^3}$ being H.

5. A compound according to claim 1, wherein
<u>Hc</u> being tetrahydropyranyl-,

whereby one or more carbon ring atom(s) thereof optionally may be substituted by one or two substituents independently selected from the group of fluorine, NC-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, C_{1-6}-alkyl-, C_{1-6}-alkyl-O- and up to one carbon ring atom may be substituted with oxo;

$\mathbf{R^1}$ being the group

V—W—*

wherein

W is selected from the group of phenyl or pyridyl,

V is selected from the group of phenyl or heteroaryl, said heteroaryl being selected from the group of oxadiazolyl, triazolyl, pyrazolyl, pyrrolyl, furanyl, pyridyl, pyrimidyl and pyridazinyl,

V preferably is attached at the 2 position of **W**, whereby the 1 position of **W** is the attachment point of **W** to the CR^2R^3 group in formula (I);

wherein **W** optionally may be substituted by one or more substituents selected from the group of fluorine, chlorine, bromine, H_3C-, F_3C-, CH_3O- and NC-, preferably selected from the group of fluorine, chlorine and F_3C-;

and wherein **V** optionally may be substituted by one or more substituents selected from the group of fluorine, chlorine, H_3C-, tert-butyl-, F_3C-, CH_3O-, cyclobutyloxy-, N-morpholinyl, benzyl-O- and NC-;

$\mathbf{R^2}$ being selected from the group of H-, fluorine, F_3C-, HF_2C-, FH_2C-, and C_{1-3}-alkyl-, preferably $\mathbf{R^2}$ being H;

$\mathbf{R^3}$ being selected from the group of H-, fluorine, F_3C-, HF_2C-, FH_2C-, and C_{1-3}-alkyl-, preferably $\mathbf{R^3}$ being H.

6. A compound according to claim 1, wherein
Hc being tetrahydropyranyl-,

whereby one or more carbon ring atom(s) thereof optionally may be substituted by one or two substituents independently selected from the group of fluorine, NC-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, C_{1-6}-alkyl-, C_{1-6}-alkyl-O- and up to one carbon ring atom may be substituted with oxo;

$\mathbf{R^1}$ being the group

V—W—*

wherein

W is phenyl whereby **W** optionally is substituted by a fluorine, chlorine or F_3C-;

V is heteroaryl being selected from the group of oxadiazolyl, triazolyl, pyrazolyl, pyrrolyl, furanyl, pyridyl, pyrimidyl and pyridazinyl, whereby

V optionally is substituted by 1 to 4, preferably 1 or 2, more preferably 1 substituent independently of each other selected from the group of fluorine, chlorine, H_3C-, *tert*-butyl-, F_3C-, CH_3O-, cyclobutyloxy-, N-morpholinyl, benzyl-O- and NC-,

V is attached at the 2 position of **W**, whereby the 1 position of **W** is the attachment point of **W** to the CR^2R^3 group in formula (I);

$\mathbf{R^2}$ being selected from the group of H-, fluorine, F_3C-, HF_2C-, FH_2C-, and C_{1-3}-alkyl-, preferably $\mathbf{R^2}$ being H;

$\mathbf{R^3}$ being selected from the group of H-, fluorine, F_3C-, HF_2C-, FH_2C-, and C_{1-3}-alkyl-, preferably $\mathbf{R^3}$ being H.

7. A compound according to claim 1, wherein
Hc being 4-tetrahydropyranyl-,

whereby each carbon ring atom thereof optionally may be substituted by one or two substituents independently selected from the group of fluorine, NC-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, C_{1-6}-alkyl-, C_{1-6}-alkyl-O- and up to one carbon ring atom may be substituted with oxo,

preferably ***Hc*** being unsubstituted 4-tetrahydropyranyl-;

$\mathbf{R^1}$ being the group

V—W—*

wherein

W is selected from the group of phenyl or pyridinyl,

V is selected from the group of phenyl or heteroaryl, said heteroaryl being selected from the group of oxadiazolyl, triazolyl, pyrazolyl, furanyl, pyridyl, pyrimidyl and pyridazinyl,

V preferably is attached at the 2 position of **W**, whereby the 1 position of **W** is the attachment point of **W** to the CR^2R^3 group in formula (I);

wherein **W** and **V** independently of each other optionally may be substituted by one or more substituents selected from the group of fluorine, chlorine, bromine, C_{1-6}-alkyl-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, F_3C-O-, HF_2C-O-, C_{3-7}-heterocycloalkyl-, H-O-C_{1-6}-alkyl-, C_{1-6}-alkyl-O-C_{1-6}-alkyl-, C_{3-7}-cycloalkyl-O-C_{1-6}-alkyl-, C_{3-7}-cycloalkyl-C_{1-3}-alkyl-O-C_{1-6}-alkyl-, phenyl-O-C_{1-6}-alkyl-, benzyl-O-C_{1-6}-alkyl-, H-O-, C_{1-6}-alkyl-O-, C_{3-7}-cycloalkyl-O-, C_{3-7}-cycloalkyl-C_{1-3}-alkyl-O-, phenyl-O-, benzyl-O-, N-morpholinyl, and NC-, preferably by a substituent selected from the group of fluorine, chlorine, bromine, C_{1-6}-alkyl-, F_3C-, F_3C-CH_2-, F_3C-O-, HF_2C-O-, C_{3-7}-heterocycloalkyl-, C_{1-6}-alkyl-O-, C_{3-6}-cycloalkyl-O-, C_{3-6}-cycloalkyl-CH_2-O-, aryl-CH_2-O- and NC-,

wherein more preferably **W** and **V** independently of each other optionally may be substituted by one or more substituents selected from the group of fluorine, chlorine,

H_3C-, F_3C-, CH_3O-, N-morpholinyl, and NC-, more preferably selected from the group of fluorine, H_3C-, F_3C-, CH_3O- and NC-;

R^2 being selected from the group of H-, fluorine, F_3C-, HF_2C-, FH_2C-, and C_{1-3}-alkyl-, preferably **R**^{2} being H;

R^3 being selected from the group of H-, fluorine, F_3C-, HF_2C-, FH_2C-, and C_{1-3}-alkyl-, preferably **R**^{3} being H.

8. A compound according to claim 1, wherein
Hc being 4-tetrahydropyranyl-,

whereby each carbon ring atom thereof optionally may be substituted by one or two substituents independently selected from the group of fluorine, NC-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, C_{1-6}-alkyl-, C_{1-6}-alkyl-O- and up to one carbon ring atom may be substituted with oxo,

preferably ***Hc*** being unsubstituted 4-tetrahydropyranyl-;

R^1 being the group

$$V—W—*$$

wherein

W is selected from the group of phenyl or pyridyl,

V is selected from the group of phenyl or heteroaryl, said heteroaryl being selected from the group of oxadiazolyl, triazolyl, pyrazolyl, pyrrolyl, furanyl, pyridyl, pyrimidyl and pyridazinyl,

V preferably is attached at the 2 position of **W**, whereby the 1 position of **W** is the attachment point of **W** to the CR^2R^3 group in formula (I);

wherein **W** optionally may be substituted by one or more substituents selected from the group of fluorine, chlorine, bromine, H_3C-, F_3C-, CH_3O- and NC-, preferably selected from the group of fluorine, chlorine and F_3C-;

and wherein **V** optionally may be substituted by one or more substituents selected from the group of fluorine, chlorine, H_3C-, *tert*-butyl-, F_3C-, CH_3O-, cyclobutyloxy-, N-morpholinyl, benzyl-O- and NC-;

$\mathbf{R^2}$ being selected from the group of H-, fluorine, F_3C-, HF_2C-, FH_2C-, and C_{1-3}-alkyl-, preferably $\mathbf{R^2}$ being H;

$\mathbf{R^3}$ being selected from the group of H-, fluorine, F_3C-, HF_2C-, FH_2C-, and C_{1-3}-alkyl-, preferably $\mathbf{R^3}$ being H.

9. A compound according to claim 1, wherein
Hc being 4-tetrahydropyranyl-,

whereby each carbon ring atom thereof optionally may be substituted by one or two substituents independently selected from the group of fluorine, NC-, F_3C-, HF_2C-,

FH_2C-, F_3C-CH_2-, C_{1-6}-alkyl-, C_{1-6}-alkyl-O- and up to one carbon ring atom may be substituted with oxo,

preferably ***Hc*** being unsubstituted 4-tetrahydropyranyl-;

R^1 being the group

V—W—*

wherein

W is phenyl whereby **W** optionally is substituted by a fluorine, chlorine or F_3C-;

V is heteroaryl being selected from the group of oxadiazolyl, triazolyl, pyrazolyl, pyrrolyl, furanyl, pyridyl, pyrimidyl and pyridazinyl, whereby

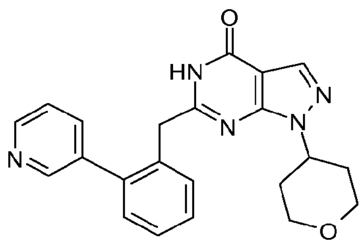
V optionally is substituted by 1 to 4, preferably 1 or 2, more preferably 1 substituent independently of each other selected from the group of fluorine, chlorine, H_3C-, *tert*-butyl-, F_3C-, CH_3O-, cyclobutyloxy-, N-morpholinyl, benzyl-O- and NC-,

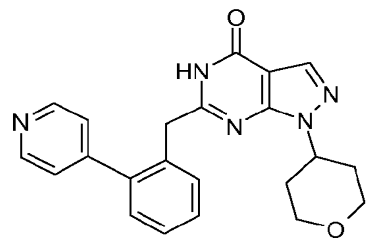
V is attached at the 2 position of **W**, whereby the 1 position of **W** is the attachment point of **W** to the CR^2R^3 group in formula (I);

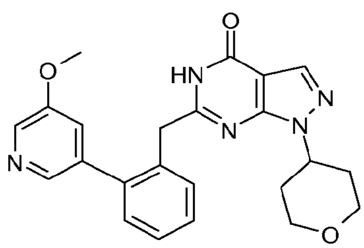
R^2 being selected from the group of H-, fluorine, F_3C-, HF_2C-, FH_2C-, and C_{1-3}-alkyl-, preferably **R^2** being H;

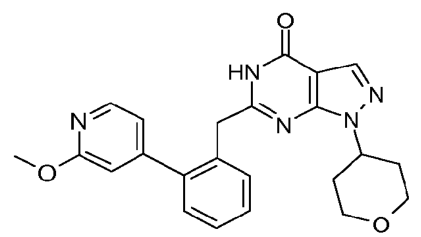
R^3 being selected from the group of H-, fluorine, F_3C-, HF_2C-, FH_2C-, and C_{1-3}-alkyl-, preferably **R^3** being H.

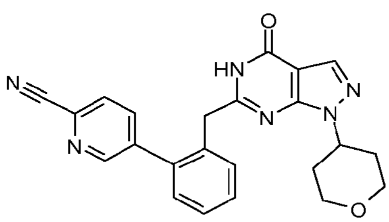
10. A compound according to claim 1, whereby the compound is selected from the group of:

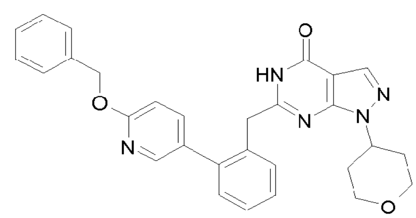
 ;

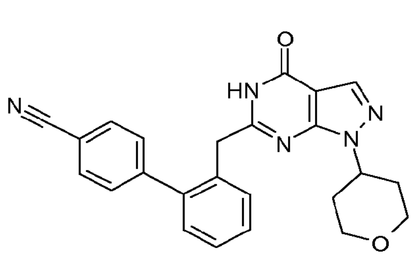
 ;

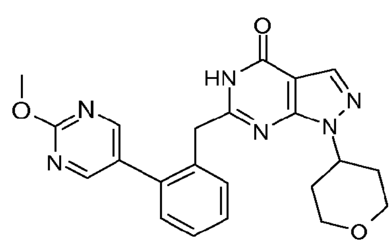
 ;

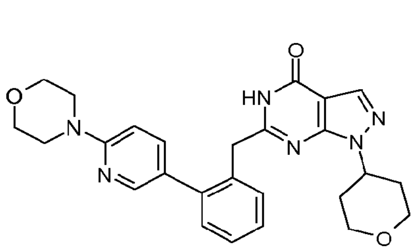
 ;

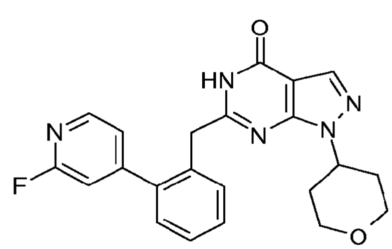
 ;

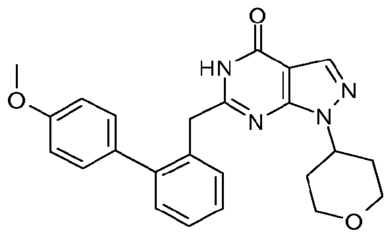
 ;

 ;

 ;

 ;

 ;



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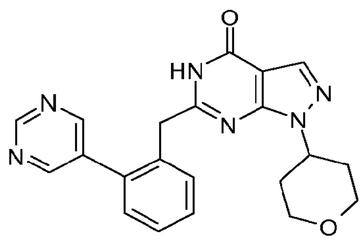

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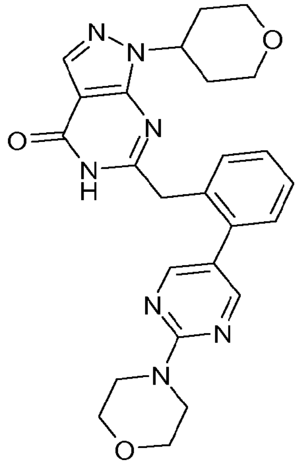

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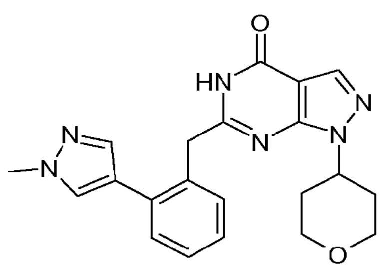

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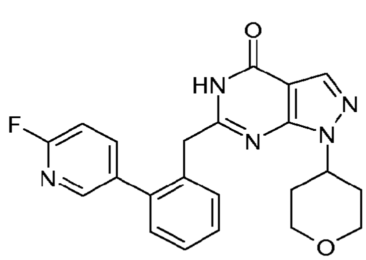

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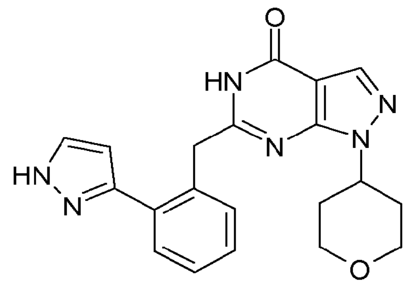

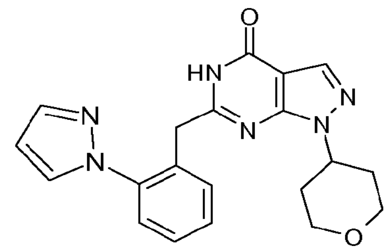

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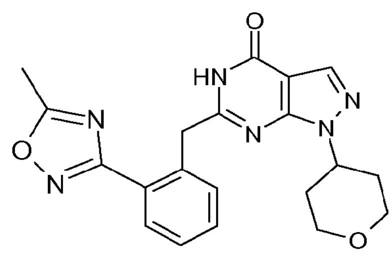

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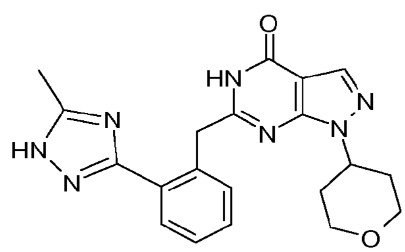

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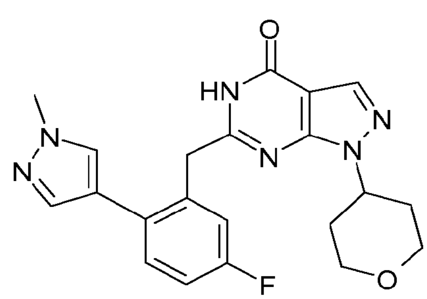

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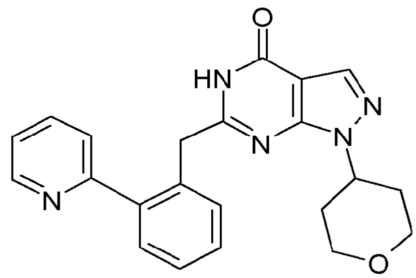
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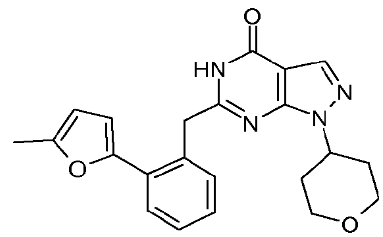
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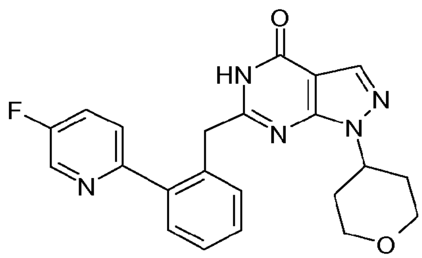
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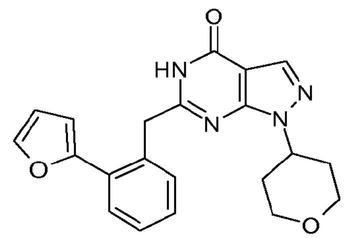
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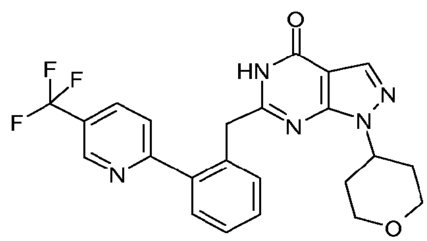
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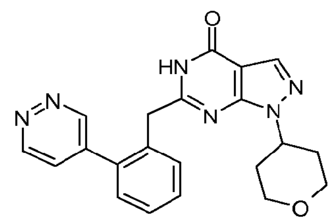
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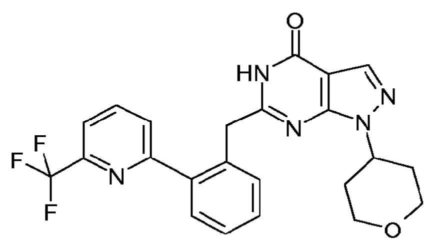
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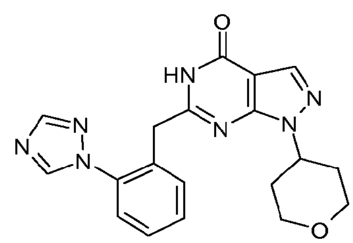
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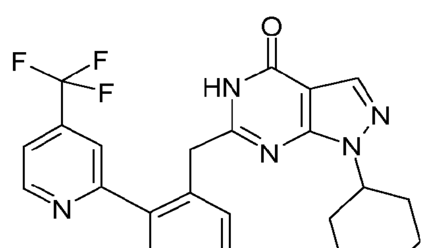
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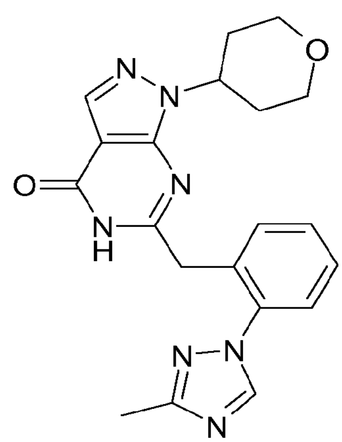
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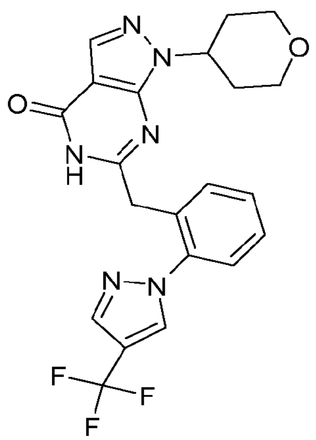

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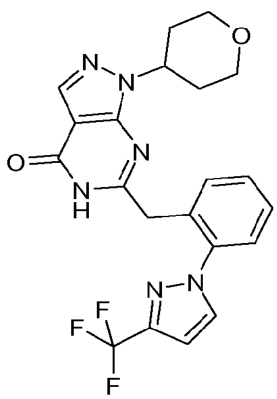

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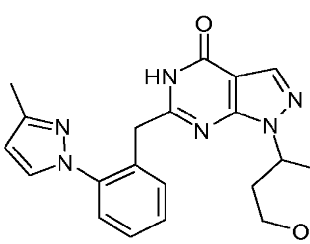

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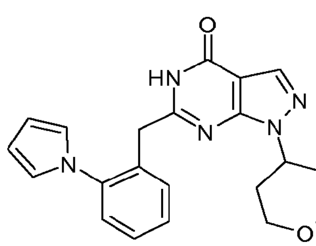

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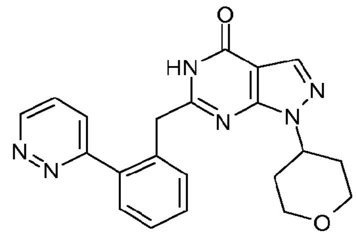

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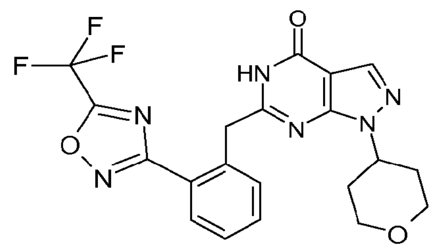

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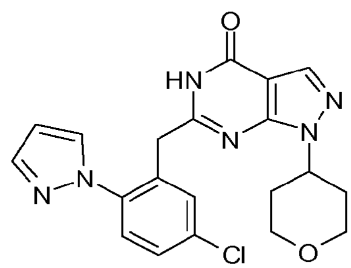

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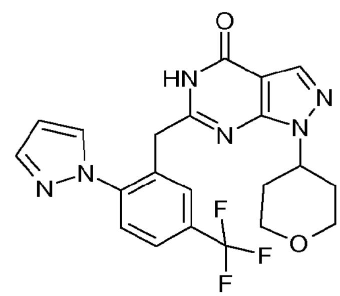

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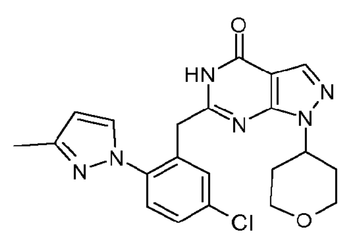

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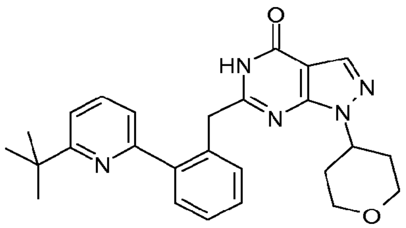

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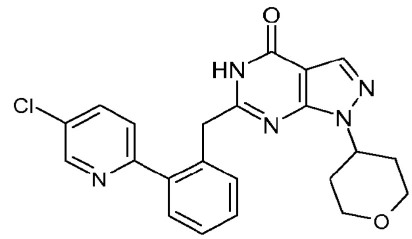

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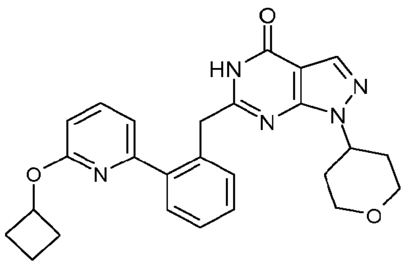

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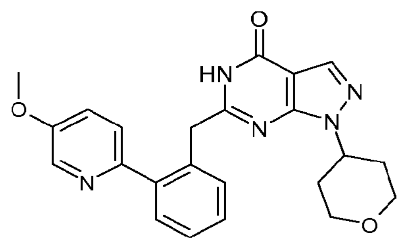

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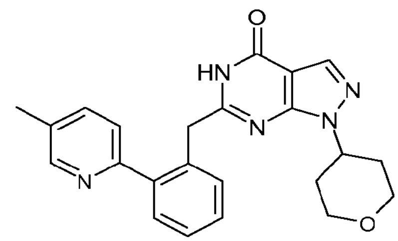

.

11. A compound according to any of claims 1 to 10 in form of a salt thereof, preferably in form of a pharmaceutically acceptable salt thereof.

12. A compound according to any of claims 1 to 11 for use as a medicament, preferably for use as a medicament for the treatment of a CNS disease, more preferably as a medicament for the treatment of a CNS disease, the treatment of which is accessible by the inhibition of PDE9.

13. Use of a compound according to claims 1 to 11 for the treatment of a disease that is accessible by the inhibition of PDE9.

14. Use of a compound according to any of claims 1 to 11 for the treatment, amelioration or prevention of cognitive impairment being related to perception, concentration, cognition, learning or memory,

preferably in patients that suffer from age-associated learning and memory impairments, age-associated memory losses, vascular dementia, craniocerebral trauma, stroke, dementia occurring after strokes (post stroke dementia), post-traumatic dementia, general concentration impairments, concentration impairments in children with learning and memory problems, Alzheimer's disease, Lewy body dementia, dementia with degeneration of the frontal lobes, including Pick's syndrome, Parkinson's disease, progressive nuclear palsy, dementia with corticobasal degeneration, amyotropic lateral sclerosis (ALS), Huntington's disease, multiple sclerosis, thalamic degeneration, Creutzfeld-Jacob dementia, HIV dementia, epilepsy, temporal lobe epilepsy, schizophrenia with dementia or Korsakoff's psychosis,

more preferably cognitive impairment being related with Alzheimer's disease and more preferably cognitive impairment being related to learning or memory in patients suffering from Alzheimer's disease.

15. Pharmaceutical composition comprising a compound according to any of claims 1 to 11 and a pharmaceutical carrier, optionally in combination with another active ingredient.

16. Pharmaceutical composition according to claim 15 for the treatment of a condition as defined by any of claims 12 to 14.

17. Method for the treatment of a condition as defined in any of claims 12 to 14 in a patient comprising administering a therapeutically active amount of a compound according to any of claims 1 to 11 to said patient in need thereof.

18. Method according to claim 17, whereby the condition is Alzheimer's disease.

19. Method according to claim 17, whereby the condition is schizophrenia.

20. Method according to claim 17, whereby the condition is epilepsy.

21. Method according to claim 17, whereby the condition is cognitive impairment associated with Alzheimer's disease.

22. Method according to claim 17, whereby the condition is cognitive impairment associated with schizophrenia.

23. Method according to claim 17, whereby the condition is cognitive impairment associated with epilepsy.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2010/054050

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D487/04 A61K31/519
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2004/018474 A (BAYER HEALTHCARE AG [DE]; HENDRIX MARTIN [DE]; BOESS FRANK-GERHARD [DE) 4 March 2004 (2004-03-04) the whole document	1-23
A	WO 2004/096811 A (PFIZER PROD INC [US]; BELL ANDREW SIMON [GB]; DENINNO MICHAEL PAUL [US) 11 November 2004 (2004-11-11) cited in the application the whole document	1-23
X,P	WO 2009/121919 A1 (BOEHRINGER INGELHEIM INT [DE]; GIOVANNINI RICCARDO [DE]; DOERNER-CIOSS) 8 October 2009 (2009-10-08) the whole document; in particular, pages 265-272, examples 219-232 and 234	1-9, 11-23

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 May 2010	06/07/2010

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Fink, Dieter

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2010/054050

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2004018474 A	04-03-2004	AU 2003258601 A1	11-03-2004
		CA 2496194 A1	04-03-2004
		DE 10238723 A1	11-03-2004
		EP 1534711 A1	01-06-2005
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		JP 2006507242 T	02-03-2006
		US 2006106035 A1	18-05-2006
WO 2004096811 A	11-11-2004	US 2004220186 A1	04-11-2004
WO 2009121919 A1	08-10-2009	PE 17562009 A1	14-12-2009